(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 December 2001 (20.12.2001)

PCT

(10) International Publication Number
WO 01/95910 A1

(51) International Patent Classification[7]: A61K 31/495, 31/50, 31/52, 31/44, A61P 31/12, C07D 471/02, 473/30, 487/02

(21) International Application Number: PCT/US01/14775

(22) International Filing Date: 8 May 2001 (08.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/211,447 13 June 2000 (13.06.2000) US
60/263,363 22 January 2001 (22.01.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/95910 A1

(54) Title: IMIDAZOPYRIDINE AND IMIDAZOPYRIMIDINE ANTIVIRAL AGENTS

(57) Abstract: The present invention concerns antiviral compounds, their methods of preparation and their compositions, and use in the treatment of viral infections. More particularly, the invention provides imidazopyridine and imidazopyrimidine derivatives (Formula I) for the treatment of respiratory syncytial virus infection.

IMIDAZOPYRIDINE AND IMIDAZOPYRIMIDINE ANTIVIRAL AGENTS

BACKGROUND OF THE INVENTION

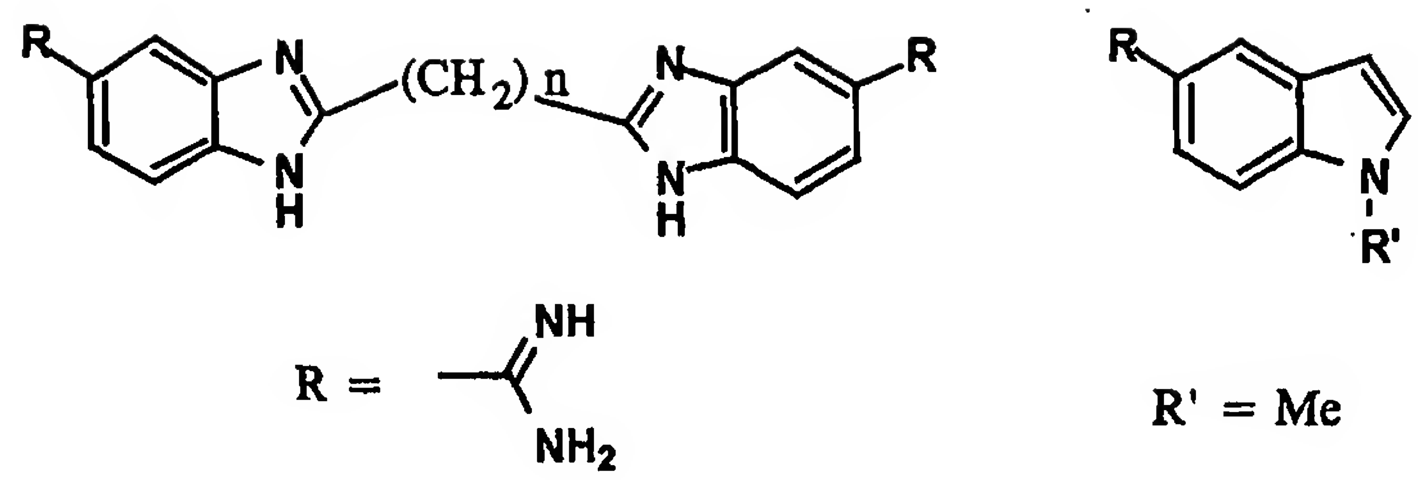
1. Field of the Invention

The present invention concerns antiviral compounds, their methods of preparation and their compositions, and use in the treatment of viral infections. More particularly, the invention provides imidazopyridine and imidazopyrimidine derivatives (Formula I) for the treatment of respiratory syncytial virus infection.

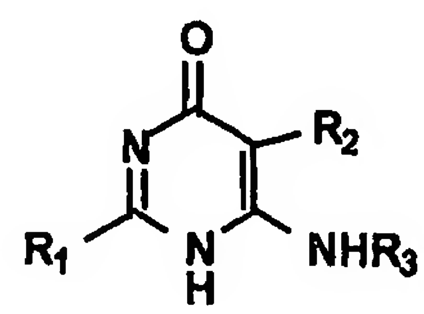
2. Background Art

Respiratory syncytial virus (RSV) is the leading cause of serious lower respiratory tract infection in infants, children, elderly and immunocompromised persons. Severe infection of the virus may result in bronchiolitis or pneumonia which may require hospitalization or result in death. (*JAMA*, 1997, *277*, 12). Currently only Ribavirin is approved for the treatment of this viral infection. Ribavirin is a nucleoside analogue which is administered intranasally as an aerosol. The agent is quite toxic, and its efficacy has remained controversial. Other than Ribavirin, RespiGam and Synagis are an immunoglobulin and monoclonal antibody, respectively, that neutralize RSV. They are the only two biologics that have been approved for prophylactic use in high risk pediatric patients for RSV infection. Both RespiGam and Synagis are very expensive and require parental administration.

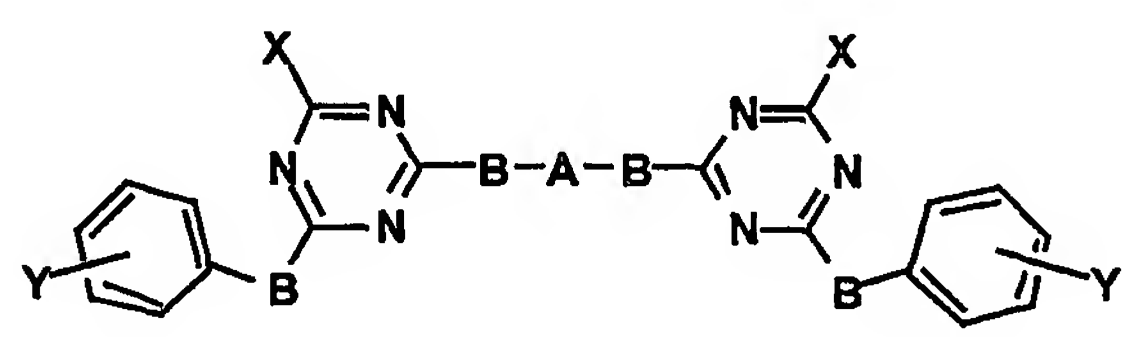
Many agents are known to inhibit respiratory syncytial virus (De Clercq, *Int. J. Antiviral Agents*, 1996, *7*, 193). Y. Tao et al. (EP 0 058 146 A1, 1998) disclosed that Cetirizine, a known antihistamine, exhibited anti-RSV activity. Tidwell et al., *J. Med. Chem.* 1983, *26*, 294 (US Patent 4,324,794, 1982), and Dubovi et al., *Antimicrobial Agents and Chemotherapy,* 1981, *19*, 649, reported a series of amidino compounds with the formula shown below as inhibitors of RSV.



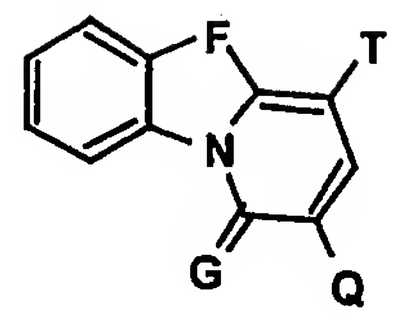
Hsu et al., US Patent 5,256,668 (1993) also disclosed a series of 6-aminopyrimidones that possess anti-viral activity against RSV.



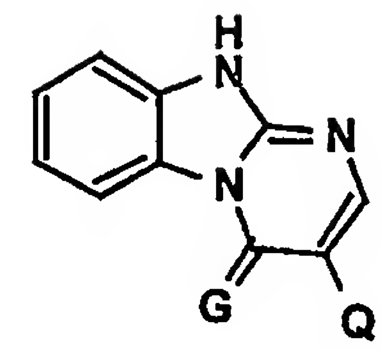
In addition, Y. Gluzman, et al., (AU Patent, Au-A-14,704, 1997) and P. R. Wyde et al. (*Antiviral Res.* 1998, *38*, 31) disclosed a series of triazine containing compounds that were useful for the treatment and/or prevention of RSV infection.



Another series of compounds structurally related to this invention are pyrido[1,2-a]benzoazoles and pyrimidio[1,2a]benzimidazoles disclosed by S. Shigeta et al in *Antiviral Chem. & Chemother.* 1992, *3*, 171. These compounds have demonstrated inhibition of orthomyxovirus and paramyxovirus replication in HeLa cells. The structures of these compounds are shown in formulas Id and Ie, in which F = NH, S, or O; Q = -NHCOPh, -COOH, COOEt, or CN; T = COMe, CN, or COOEt; G = O or NH.

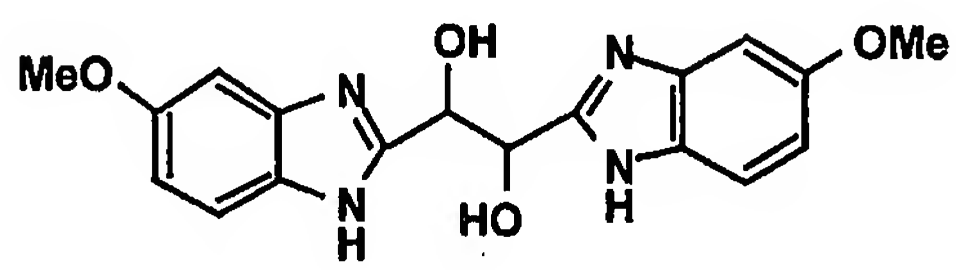


Formula Id

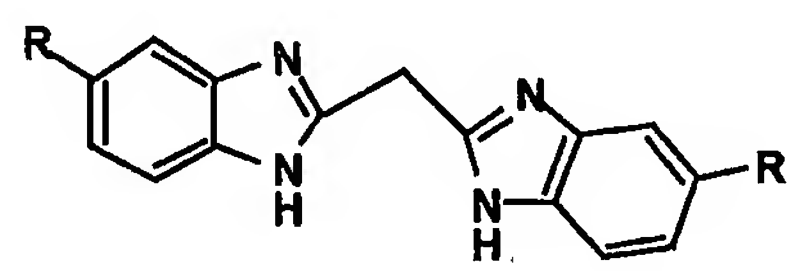


Formula Ie

A bis-benzimidazole with an ethylenediol linker shown below has also been reported as a potent inhibitor of rhinoviruses (Roderick, et al. *J. Med. Chem.* 1972, *15*, 655).

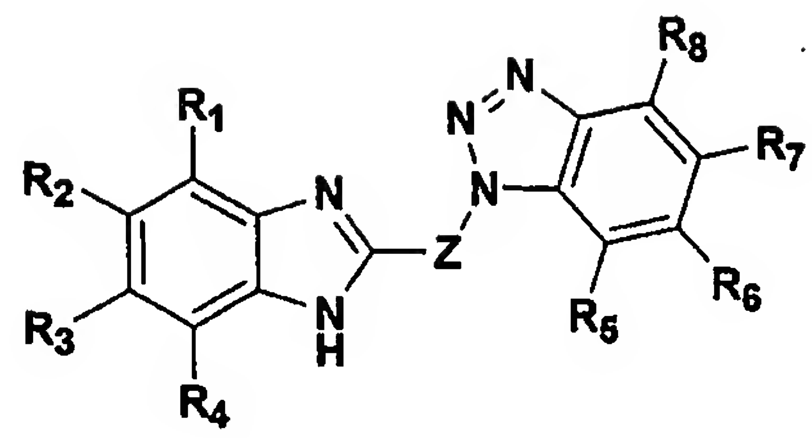


Other structurally related compounds are bis-benzimidazoles which possess antifungal activity (B. Cakir, et al. *Eczacilik Fak. Derg.* 1988, *5*, 71).

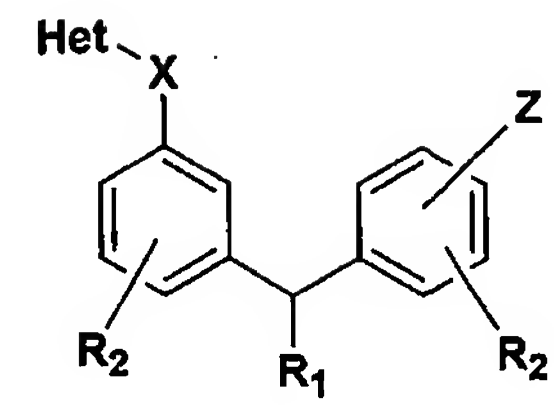


R = H, NO_2

Most recently Yu et al. have discovered a series of benzimidazoles (Formula II) for the treatment and prevention of RSV infection (WO 00/04900). In addition, Theodore Nitz has also found a series of compounds with Formula III that inhibit RSV in Hep-2 cell tissue culture assay (WO 99/38508). Although many other agents are known to inhibit respiratory syncytial virus (De Clercq, *Int. J. Antiviral Agents*, 1996, 7, 193) none of them have been used in human clinical trials. Thus, there is a medical need for a convenient and less expensive anti-viral agent for the treatment and prevention of RSV infection.



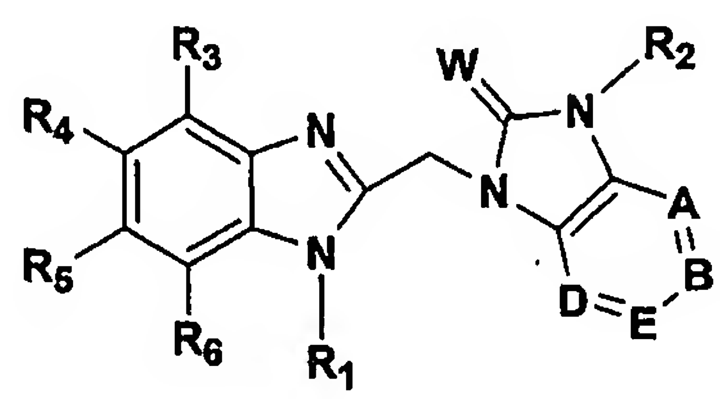
Formula II



Formula III

SUMMARY OF THE INVENTION

This invention relates to compounds having the Formula I, and pharmaceutically acceptable salts thereof



Formula I

wherein:

W is O or S;

R_1 is -(CR'R")$_n$-X;

X is H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR"", NR'R", NR'COR", NR'CONR"R"', NR'SO_2R", NR'COOR", COR', CR"'NNR'R", CR'NOR", COOR', CONR'R", SO_mR', PO(OR')$_2$, aryl, heteroaryl or non-aromatic heterocycle;

m is 0-2; n is 2-6;

R_2 is

(i) H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, $-(CH_2)_t$ C_{3-7} cycloalkyl, $-(CH_2)_t$ C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; SO_2R'', $SO_2NR'R''$ or CN; wherein t is 1-6;

(ii) $-(CR'R'')_{n'}$-Y, wherein Y is CN, OR', OCONR'R", NR'R", NCOR', $NR'SO_2R''$, NR'COOR", NR'CONR"R"', COR', CR"'NNR'R", CR'NOR", COOR', CONR'R", SO_mR', $SO_2NR'R''$ or $PO(OR')_2$; wherein

m is 0-2 and n' is 1-6;

(iii) $-(CR'R'')_{n''}$-C_6H_4-Z, wherein the Z group may be in the ortho, meta or para position relative to the $-(CH_2)_{n''}$ group; Z is CN, OR', OCONR'R", NO_2, NR'R", NCOR', $NR'SO_2R''$, NR'COOR", NR'CONR"R"', COR', CR"'NNR'R", CR'NOR", COOR', CONR'R", SO_mR', $SO_2NR'R''$ or $PO(OR')_2$;

m is 0-2; n" is 0-6; or

(iv) -(CR'R")n"'-heteroaryl, wherein n"' is 0-6;

(v) -(CR'R")n"'-non-aromatic heterocycle, wherein n"' is 0-6;

R_3, R_4, R_5 and R_6 are each independently hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkyl substituted with one to six of the same or different halogen atoms, OR', CN, COR', COOR', CONR'R", or NO_2;

A, B, E, D are each independently C-H, C-Q-, N, or N-O; provided at least one of A, B, E or D is not C-H or C-Q; wherein Q is halogen, C_{1-3} alkyl or C_{1-3} alkyl substituted with one to three of the same or different halogen atoms; and

R', R'', R''' are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms;or R' and R'' taken together form a cyclic alkyl group having 3 to 7 carbon atoms; benzyl or aryl ;

R'''' is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, NR'R'', CR'NR''R''', aryl, heteroaryl, non-aromatic heterocycle; and

Non-aromatic heterocycle is a 3-7 membered non-aromatic ring containing at least one and up to 4 non-carbon atoms selected from the group consisting of O, S, N, and NR';

Aryl is phenyl, naphthyl, indenyl, azulenyl, fluorenyl and anthracenyl;

Heteroaryl is a 4-7 membered aromatic ring which contains one to five heteroatoms independently selected from the group consisting of O, S, N or NR', wherein said aromatic ring is optionally fused to group B';

B' is an aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl;

Aryl, B', said 4-7 membered aromatic ring, and said 3-7 membered non-aromatic ring may each independently contain one to five substituents which are each independently selected from R_7, R_8, R_9, R_{10} or R_{11}; and

R_7, R_8, R_9, R_{10} and R_{11} are each independently

(i) H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; and

(ii) halogen, CN, NO_2, OR', NR'R'', COR', COOR', CONR'R'', OCOR', NR'COR'', SO_mR', $SO_2NR'R''$, $PO(OR')_2$.

A preferred embodiment includes compounds of Formula I wherein heteroaryl is selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-oxadiazol-5-one, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, tetrazole and phenoxazinyl.

Another preferred embodiment includes compounds of Formula I wherein:

R_1 is $-(CH_2)_n-X$;

X is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR'''', NR'R'', NR'COR'', NR'COOR'', COR', CR'''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', aryl or heteroaryl;

m is 0-2; n is 2-4;

R_2 is

(i) H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, $-(CH_2)_t$ C_{3-7} cycloalkyl, $-(CH_2)_t$ C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; SO_2R'', $SO_2NR'R''$ or CN; wherein t is 1-6;

(ii) $-(CH_2)_{n'}-Y$, wherein Y is CN, OR', COR', COOR', CONR'R'', SO_mR', $SO_2NR'R''$, $PO(OR')_2$ wherein m is 0-2 and n' is 1-6; or

(iii) $-(CH_2)n''-C_6H_4-Z$, wherein the Z group may be in the ortho, meta or para position relative to the $-(CH_2)n''$ group; Z is CN, OR', COR' or SO_mR'; m is 0-2; n'' is 0-3;

R_3, R_4, R_5, and R_6 are each independently hydrogen, halogen, C_{1-6} alkyl, optionally substituted with one to six of the same or different halogen atoms; and

A, B, E, D are each independently C-H or N; provided at least one of A, B, E or D is not C-H.

Another preferred embodiment includes compounds of Formula I wherein:

R_3, R_4, R_5 and R_6 are each H;

A, B and D are each C-H; and

E is N.

Another preferred embodiment includes compounds of Formula I wherein:

R_3, R_4, R_5 and R_6 are each H;

A, B and E are each C-H; and

D is N.

In another embodiment of the invention there is provided a method for treating mammals infected with RSV, and in need thereof, which comprises administering to said mammal a therapeutically effective amount of one or more of the aforementioned compounds of having Formula I, including pharmaceutically acceptable salts thereof.

Another embodiment includes a pharmaceutical composition which comprises a therapeutically effective amount of one or more of the aforementioned anti-RSV compounds having Formula I, including pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

The term pharmaceutically acceptable salt includes solvates, hydrates, acid addition salts and quarternary salts. The acid addition salts are formed from a compound of Formula I and a pharmaceutically acceptable inorganic or organic acid including but not limited to hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, acetic, citric, malonic, fumaric, maleic, oxalic acid, sulfamic, or tartaric acids. Quaternary salts include chloride, bromide, iodide, sulfate, phosphate, methansulfonate, citrate, acetate, malonate, fumarate, oxalate, sulfamate, and tartrate. Halogen means bromine, chlorine, fluorine and iodine.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions apply unless indicated otherwise:

An "aryl" group refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, napthalenyl and anthracenyl.

As used herein, a "heteroaryl" group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzthiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, and pyrazinyl.

As used herein, a "non-aromatic heterocycle" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of non-aromatic heterocycle groups are azetidinyl, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, oxazolidonyl, oxazolonyl, 2-pyrrolidinonyl, hydantoinyl, meleimidyl and oxazolidinedionyl.

An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., "1-20", is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More

preferably, it is a medium size alkyl having 1 to 10 carbon atoms. For example, the term "C_{1-6} alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like.

A “cycloalkyl” group refers to a saturated all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, and adamantane.

A “cycloalkenyl” group refers to an all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings contains one or more carbon-carbon double bonds but does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkenyl groups are cyclopentene, cyclohexadiene, and cycloheptatriene.

An “alkenyl” group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond.

An “alkynyl” group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond.

A “hydroxy” group refers to an –OH group.

An “alkoxy” group refers to both an –O-alkyl and an –O-cycloalkyl group as defined herein.

An “O-carboxy” group refers to a R”C(O)O-group, with R” as defined herein.

An “amino” group refers to an $-NH_2$ group.

A "N-amido" group refers to a $R^xC(=O)NR^y$- group, with R^x selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, and heteroalicyclic and R^y selected from hydrogen or alkyl.

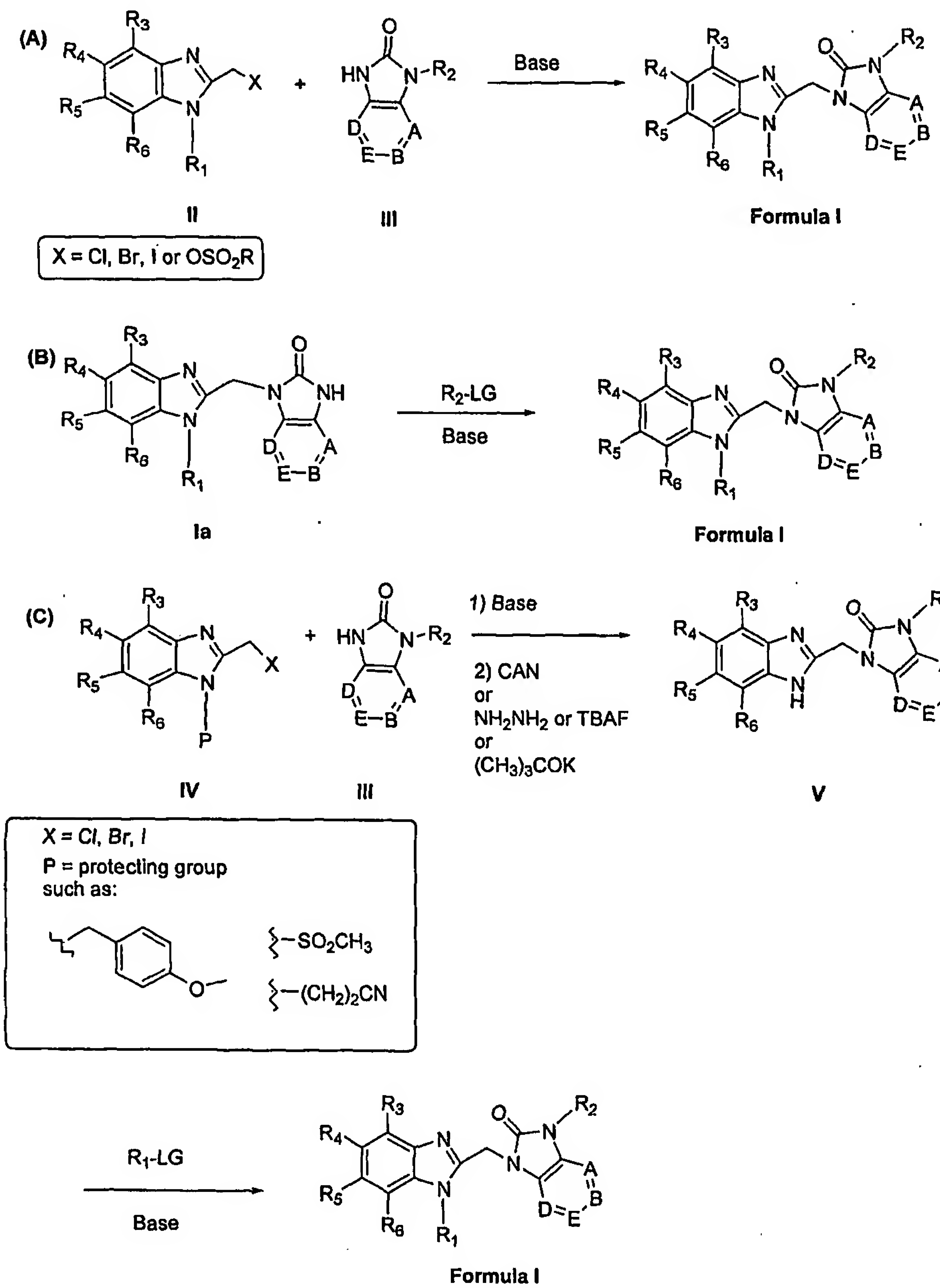
A "cyano" group refers to a –CN group.

It is known in the art that nitrogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present invention are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

Compounds of Formula **I** can be prepared either by coupling 2-substituted-benzimidazoles (**II**), where X is a halide or sulfonate such as mesylate or tosylate, with 2-oxo-imidazopyridines or 2-oxo-imidazopyrimidines (**III**) in the presence of base, preferably phosphazene bases such as t-butylimino-tri(pyrrolidino)phosphorane (BTPP), cesium carbonate or sodium hydride (Scheme I-A) or by reacting **Ia** with a R_2-LG, where LG is a leaving group, preferably a halide or sulfonate such as mesylate or tosylate (Scheme I-B). Alternatively, compounds of Formula **I** can be synthesized according to the procedure described in Scheme I-C. Coupling of 2-substituted-benzimidazoles (**IV**) containing protecting groups (P) such as p-methoxybenzyl, mesyl, or 2-cyanoethyl with 2-oxo-imidazopyridines or 2-oxo-imidazopyrimidines in the presence of base is followed by removal of the protecting group using appropriate conditions. Deprotection can be accomplished by treatment with ceric ammonium nitrate (CAN), treatment with hydrazine or tetrabutylammonium fluoride (TBAF), or treatment with potassium *tert*-butoxide to respectively remove p-methoxybenzyl, mesyl, or 2-cyanoethyl groups and give intermediates **V**. Compounds of Formula I can then be prepared by reacting **V** with R_1-LG

where LG is a leaving group preferably a halide or sulfonate such as mesylate or tosylate.

Scheme I: Preparation of Formula I

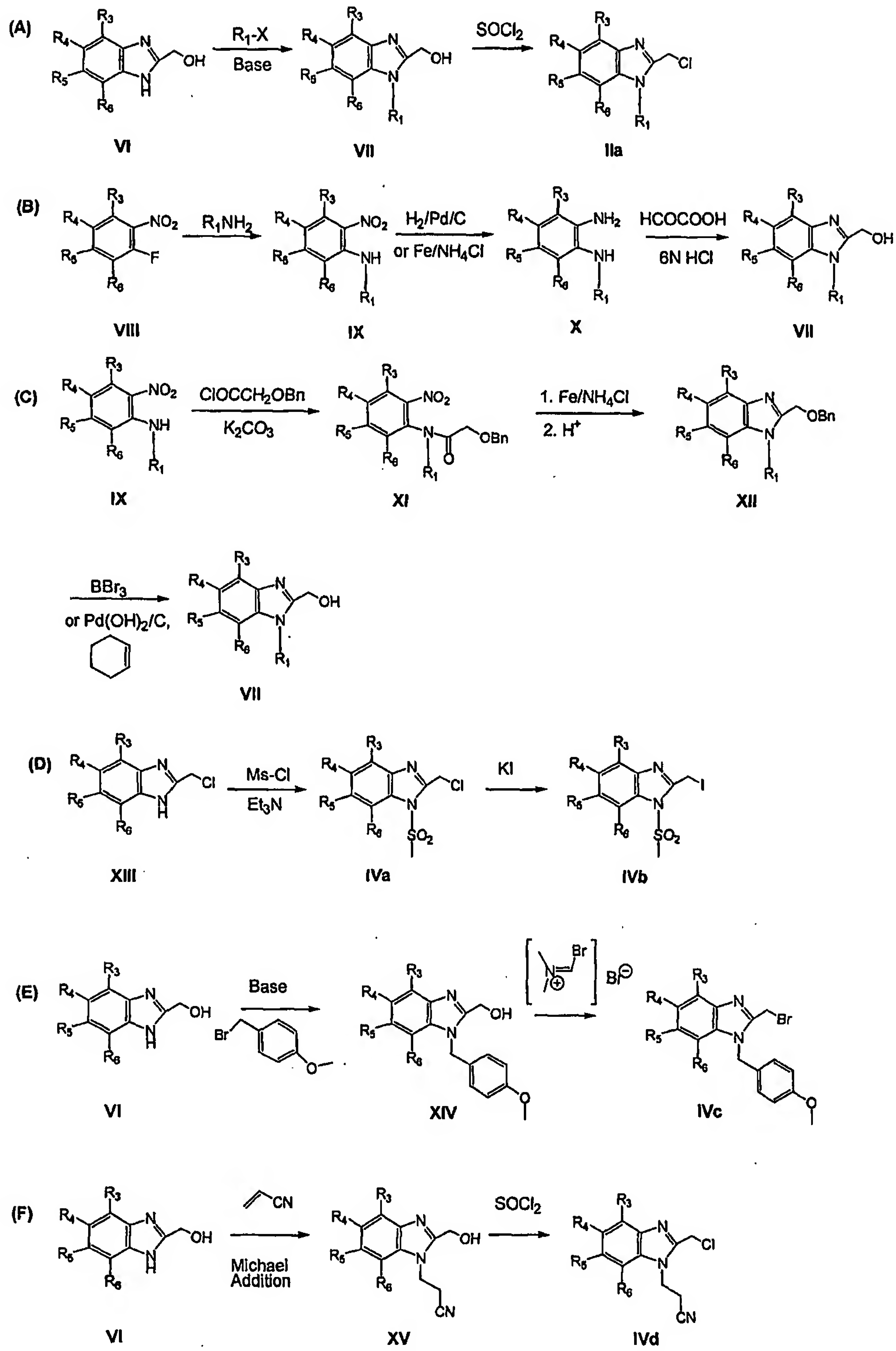


The synthesis of 2-substituted-benzimidazoles (**IIa**) is shown in Schemes II A-C. Treatment of substituted or unsubstituted 2-hydroxymethylbenzimidazole

(**VI**) with 1.05 equivalents of base, preferably sodium hydride or cesium carbonate, followed by the addition of R_1-LG, where LG is a leaving group such as halide or sulfonate, gives compound **VII**. Treatment of the alcohol with thionyl chloride provides 2-chloromethyl-benzimidazole **IIa** (Scheme II-A). In a separate synthetic route, depicted in Scheme II-B, 2-fluoro-nitrobenzene (**VIII**) reacts with an amine to afford compound **IX**. Reduction of the nitro group provides a phenylenediamine derivative **X** which is cyclized with glycolic acid in 4-6 N HCl to give alcohol **VII**. Alternatively, 2-amino-nitrobenzene (**IX**) is acylated with 2-benzyloxyacetyl chloride to provide **XI** (Scheme II-C). Reduction of the nitro group followed by ring closure in ethanol in the presence of catalytic amount of acetic acid provides **XII**. Removal of the benzyl group using boron tribromide or palladium hydroxide on carbon and cyclohexene yields **VII**.

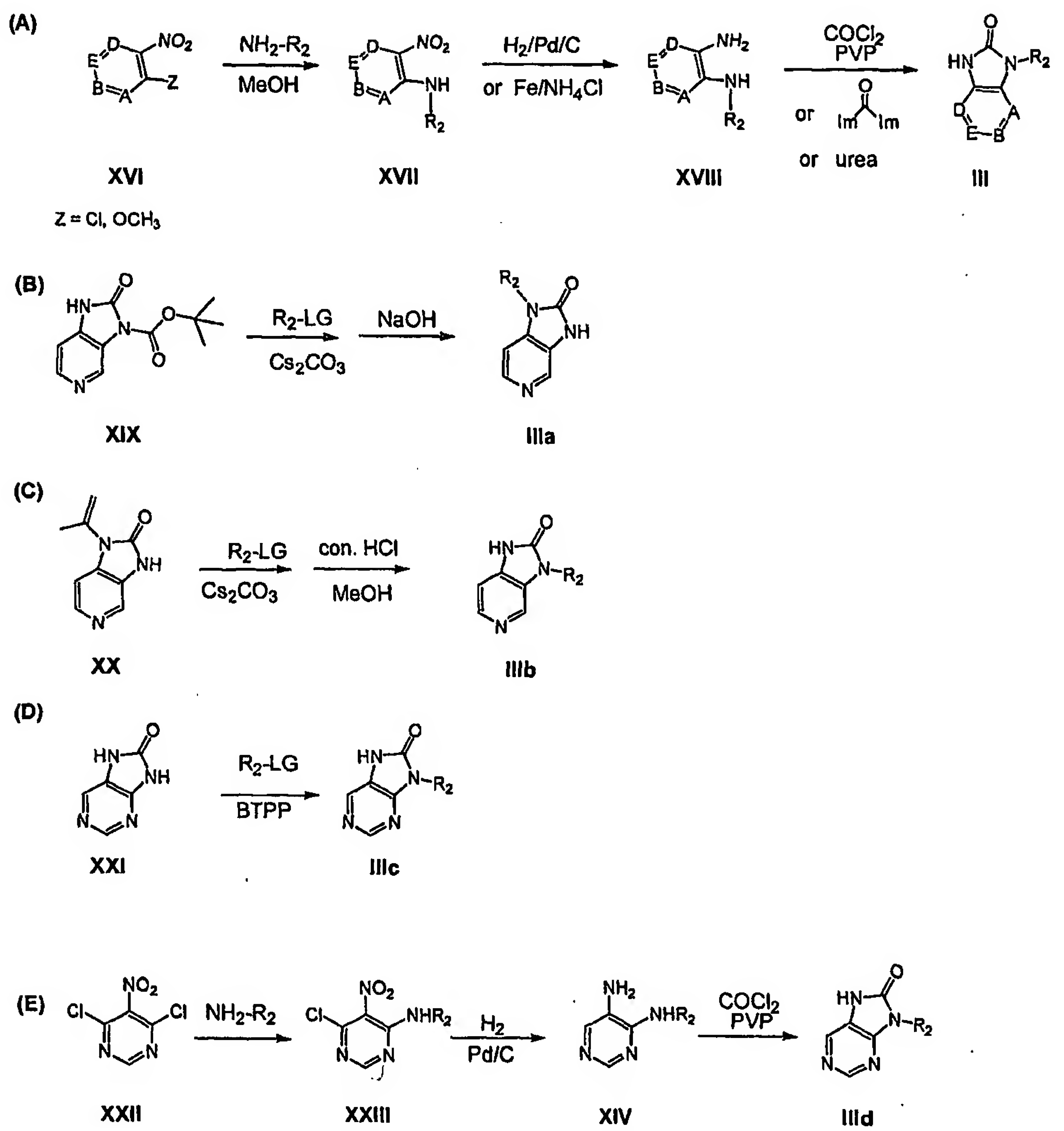
Preparation of compounds **IVa** – **IVd** containing protecting groups is depicted in Schemes II D-F. In Scheme II-D, 2-chloromethylbenzimidazole reacts with methane sulfonyl chloride (Ms-Cl) and triethylamine to give compound **IVa**. The chloride can be refluxed with potassium iodide in acetone to produce compound **IVb**. A *p*-methoxybenzyl protecting group is installed in Scheme II-E. Reaction of 4-methoxybenzyl chloride with 2-hydroxymethyl benzimidazole (**VI**) in the presence of base, preferably sodium hydride, gives compound of Formula **XIV**. Treatment of alcohol **XIV** with (bromomethylene)dimethylammonium bromide provides compound **IVc**. Compound **IVd** can be prepared as described in Scheme II-F. Michael addition of 2-hydroxymethylbenzimidazole (**VI**) with acrylonitrile yields compound **XV** which is then converted to the chloride **IVd** by treatment with thionyl chloride.

Scheme II: Preparation of Benzimidazoles Ia



2-Oxo-imidazopyridines and 2-oxo-imidazopyrimidines can be synthesized using the procedure depicted in Scheme III. Displacement of Z, which is a halide, preferably chlorine, or an alkoxy group, preferably methoxy, of nitropyridines **XVI** (2-chloro-3-nitro-pyridine, 4-alkoxy-3-nitropyridine and 3-alkoxy-2-nitropyridine) with an amine gives **XVII** (Scheme III-A). Reduction of the nitro group and cyclization of the resulting diamine (**XVIII**) using phosgene/polyvinylpyridine, carbonyldiimidazole or urea provides N3-substituted 2-oxo-imidazopyridine ***III*** . N-substituted 2-oxo-5-imidazo-pyridines **IIIa** are prepared from known compound **XIX** by N-alkylation and deprotection of the *t*-butoxycarbonyl with aqueous sodium hydroxide (Scheme III-B). On the other hand, N-alkylation of **XX** and acid hydrolysis of the isopropenyl group gives 2-oxo-imidazo-6-pyridine **IIIb** (Scheme III-C). 2-Oxo-imidazopyrimidines (**IIIc**) can be prepared directly by reacting 2-oxo-imidazopyrimidine (**XXI**) with R_2-LG where LG is a leaving group as described above, to give **IIIc,** as illustrated in Scheme III-D. Alternatively, 4,6-dichloro-5-nitropyrimidine (**XXII**) is treated with an amine to generate **XXIII** (Scheme III-E). Catalytic reduction of both the nitro group and the carbon-chlorine bond, and cyclization of the resulting diamine (**XIV**) with phosgene provides **IIId**.

Scheme III: Preparation of 2-oxo-imidazopyridines and 2-oxo-imidazopyrimidines



Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 500, AC-300, Bruker DPX-300 or a Varian Gemini 300 spectrometer. All spectra were determined in $CDCl_3$, CD_3OD, or DMSO-d_6 and chemical shifts are reported in δ units relative to tetramethylsilane (TMS). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad peak; dd, doublet of doublets; dt, doublet of triplets. Mass

spectroscopy was performed on a Finnigan SSQ 7000 quadrupole mass spectrometer in both positive and negative electrospray ionization (ESI) modes or on a LC-MS using Shimadzu LC-10AS with micromass platform LC single quadrupole mass spectrometer in positive electrospray ionization. High resolution mass spectroscopy was recorded using a Finnigan MAT 900. Infrared (IR) spectra were recorded on a Perkin-Elmer system 2000 FT-IR. Elemental analysis was performed with a Perkin-Elmer series II, model 2400 CHN/O/S analyzer. Column chromatography was performed on silica gel from VWR Scientific. Preparative HPLC was performed using a Shimadzu LC-8A on a C18 column eluted with mixture of MeOH in water with 0.1 % trifluoroacetic acid.

Abbreviations used in the experimental section:

BEMP: 2-*t*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine

BTPP: *t*-butylimino-tri(pyrrolidino)phosphorane

CAN: ceric ammonium nitrate

DBU: 1,8-diazabicyclo[5,4,0]undec-7-ene

DIEA: *N,N*-diisopropylethylamine

DMF: dimethylformamide

DMSO: dimethyl sulfoxide

Et_2O: diethyl ether

EtOAc: ethyl acetate

EtOH: ethyl alcohol

MeOH: methanol

Prep HPLC: preparative high performance liquid chromatography

Prep TLC: preparative thin layer chromatography

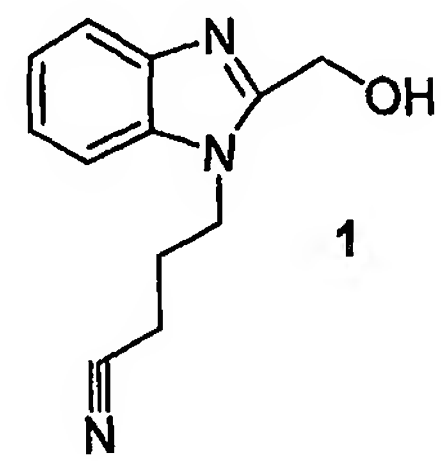
TBAF: tetrabutylammonium fluoride

TFA: trifluoroacetic acid

THF: tetrahydrofuran

I. Preparation of Benzimidazoles:

Compounds **1-25**, **59-111**, and **138-143** are benzimidazole intermediates synthesized according to the procedures described in Scheme II.



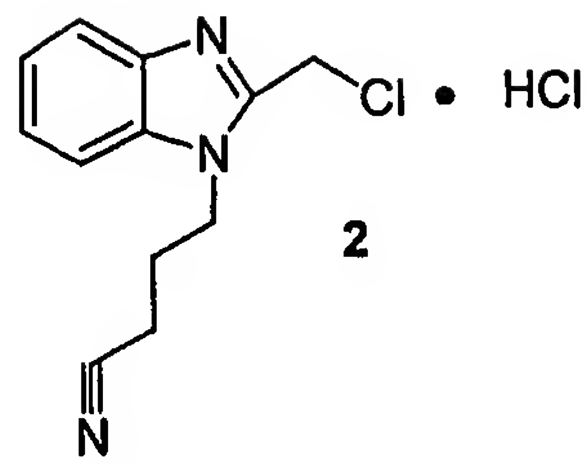
1

To a solution of 2-hydroxymethylbenzimidazole (29.63 g, 200 mmol) in a mixture of DMF/THF (150 mL, 1:1) was added sodium hydride (60% in mineral oil, 8.4 g, 210 mmol) in several portions at room temperature. After stirring for 1 hour, 4-bromobutyronitrile (29.6 g, 200 mmol) was added and the resulting solution was stirred at 80 °C for 16 hours. The solvent was evaporated and the residue diluted with water and extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:1 to 2:1, then EtOAc/MeOH, 10:1) to give 22.11 g (51% yield) of **1** as a white solid.

^{1}H NMR ($CDCl_3$) δ 2.27-2.32 (m, 2 H), 2.41 (t, J = 6.0 Hz, 2 H), 4.41 (t, J = 7.2 Hz, 2 H), 7.26-7.38 (m, 3 H), 7.67-7.70 (m, 1 H);
MS m/e 216 (MH^+).

General Procedure for Converting 2-Hydroxymethyl-benzimidazoles to 2-Chloromethyl-benzimidazoles.

The procedure described below was used for the synthesis of compounds **2, 4, 9, 11A+11B, 15, 19, 23, 25, 70, 72, 76, 81, 88, 92, 94, 96, 98, 100, 102, 108,** and **111** and **143**.



2

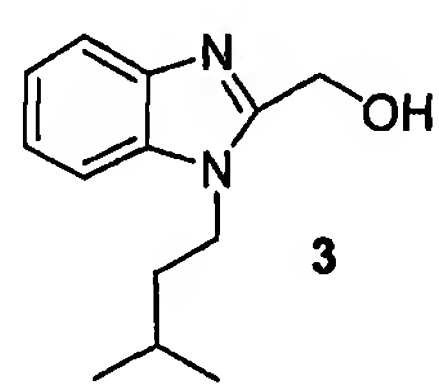
To alcohol **1** (22 g, 102.2 mmol) suspended in CH_2Cl_2 (100 mL),thionyl chloride (15.81 g, 132.9 mmol) was slowly added with ice-water bath cooling. The ice bath was removed. The solution was stirred at room temperature for 1 hour and then evaporated. The residue was triturated with EtOAc to give a nearly quantitative yield of **2** as light gray powder.

^{1}H NMR ($CDCl_3$) δ 2.32-2.38 (m, 2 H), 2.70 (t, J = 7.3 Hz, 2 H), 4.69 (t, J = 7.6 Hz, 2 H), 5.33 (s, 2 H), 7.69-7.74 (m, 2 H), 7.85-7.87 (m, 1 H), 8.00-8.02 (m, 1 H);

MS m/e 234 (MH^+).

Anal. Calcd for $C_{12}H_{12}N_3$•HCl•0.25 H_2O: C, 52.48; H, 4.95; N, 15.30

Found: C, 52.52; H, 4.88; N, 15.26

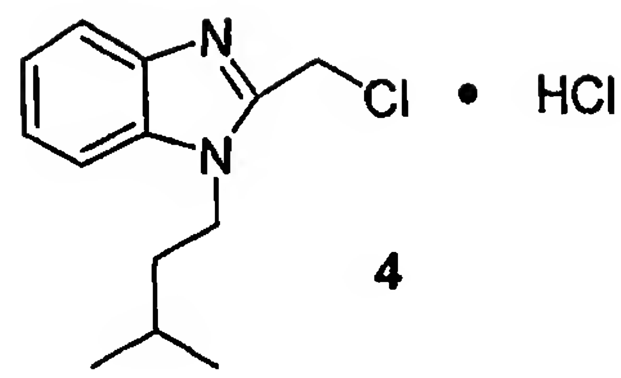


3

Compound **3** was prepared using the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with 3-methylbutylbromide.

^{1}H NMR ($CDCl_3$) δ 1.71-1.78 (m, 3 H), 4.28 (t, J = 7.5 Hz, 2 H), 5.02 (s, 2 H), 7.33-7.41 (m, 3 H), 7.75 (d, J = 7.9 Hz, 2 H);

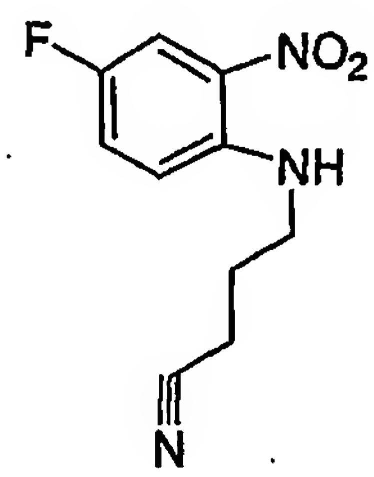
MS m/e 219 (MH^+).



4

Compound **4** was prepared according to the same procedure described for compound **2.**

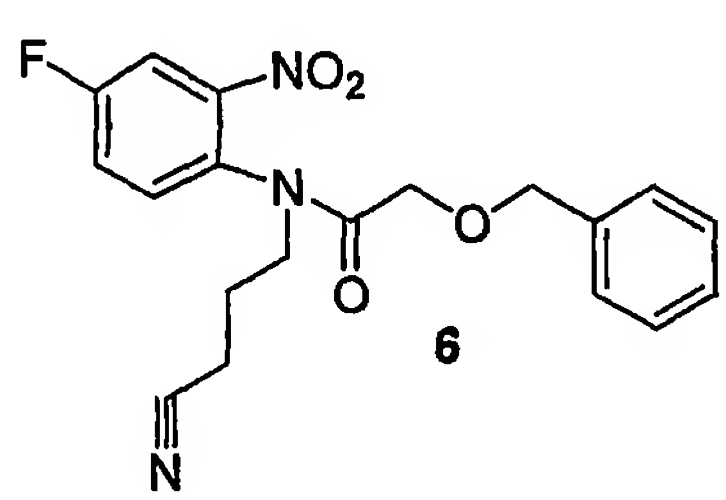
^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 6.4 Hz, 6 H), 1.83-1.89 (m, 3 H), 4.57-4.60 (m, 2 H), 5.30 (s, 2 H), 7.68-7.73 (m, 2 H), 7.84-7.86 (m, 1 H), 7.93-7.95 (m, 1H); MS m/e 237 (MH^+).



5

A solution of 2,5-difluoronitrobenzene (15.4 g, 96.8 mmol), 4-aminobutyronitrile (7.4 g, 88 mmol) and diisopropylethylamine (23 ml, 132 mmol) in DMF (250 ml) was stirred at room temperature for 32 hours. After filtration, the solvent was evaporated and the orange solid was recrystallized from MeOH (250 ml) to afford **5** (14 g, 65% yield) as orange crystals.

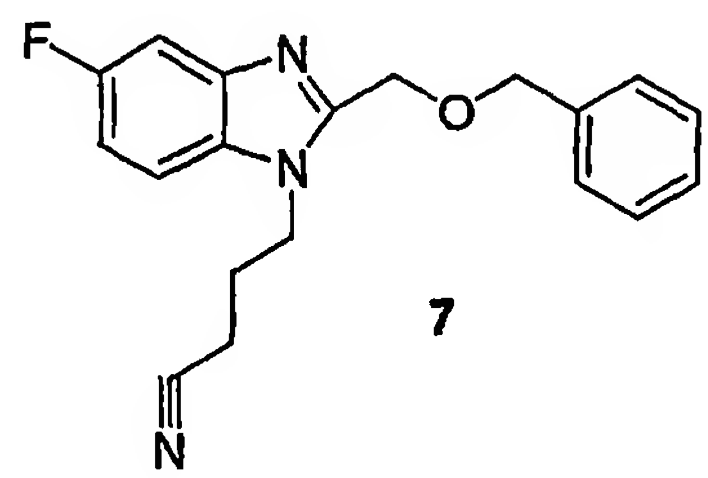
^{1}H NMR ($CDCl_3$) δ 2.06-2.12 (m, 2 H), 2.54 (t, J = 7.0 Hz, 2 H), 3.48-3.53 (m, 2 H), 6.85-6.88 (m, 1 H), 7.27-7.31 (m, 1 H), 7.89-7.92 (m, 1 H); MS m/e 224 (MH^+).



6

To a suspension of nitrile **5** (10.8 g, 48.4 mmol) and potassium carbonate (20.1 g, 145 mmol) in CH_3CN (200 ml) was added benzyloxyacetyl chloride (7.64 ml, 48.4 mmol) dropwise. After stirring at room temperature for 12 hours, the mixture was diluted with EtOAc (500 ml) and filtered. The filtrate was washed with 1 N HCl, brine, dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:2 to 1:1) to yield **6** (7.5 g, 42% yield) as a viscous pale yellow oil.

^{1}H NMR ($CDCl_3$) δ 1.86-1.98 (m, 2 H), 2.38-2.51 (m, 2 H), 3.34-3.39 (m, 1 H), 3.80-3.87 (m, 2 H), 4.06-4.14 (m, 1 H), 4.40-4.48 (m, 2 H), 7.18-7.19 (m, 1 H), 7.26-7.40 (m, 5 H), 7.72-7.74 (m, 1 H);
MS m/e 394 (MH^+).

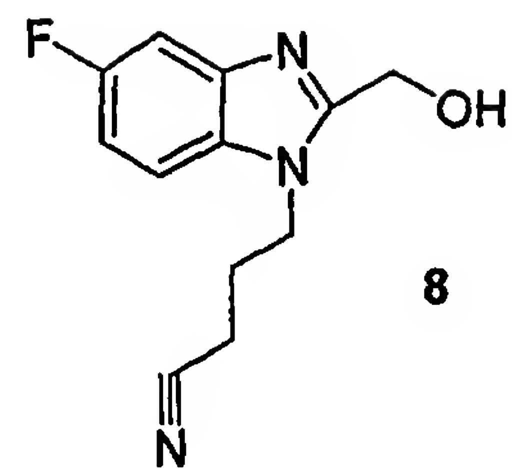


7

In a flask equipped with a mechanical stirrer, a suspension of compound **6** (6.40 g, 17.25 mmol), iron powder (2.89 g, 51.8 mmol) and ammonium chloride (4.61 g, 86.2 mmol) in a mixture of MeOH and H_2O (200 ml, 1:1) was stirred at reflux for 4 hours. The mixture was filtered through a pad of Celite and washed with MeOH. The filtrate was evaporated and the residue was taken up in EtOAc (500 ml), washed with brine, dried over $MgSO_4$, and evaporated. To the residue was added CH_3CN (100 ml) and acetic acid (1 ml), and the mixture was stirred at reflux for 4 hours. The solvent was evaporated and the residue was purified by flash chromatography (gradient, EtOAc/hexane, 1:2 to 2:1) to give **7** (4.42 g, 75% yield) as a viscous oil which solidified upon standing.

^{1}H NMR ($CDCl_3$) δ 2.15-2.20 (m, 2 H), 2.31 (t, J = 7.0 Hz, 2 H), 4.35 (t, J = 7.2 Hz, 2 H), 4.62 (s, 2 H), 4.83 (s, 2 H), 7.07-7.11 (m, 1 H), 7.29-7.38 (m, 6 H), 7.43-7.46 (dd, J = 2.4, 9.2 Hz, 1 H);

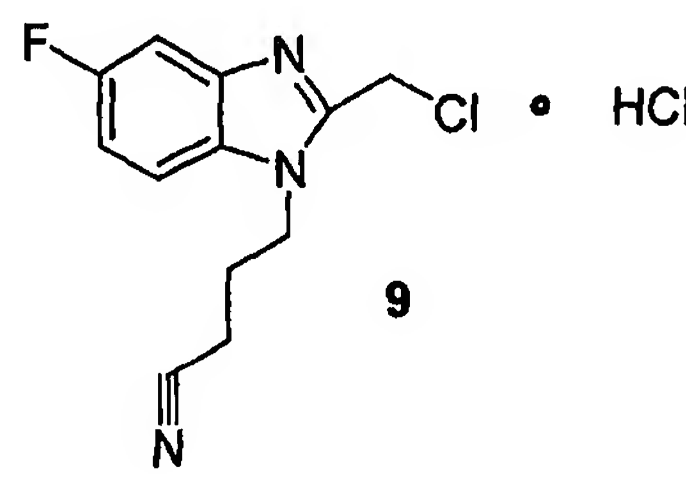
MS m/e 324 (MH^+).



8

To a solution of 7 (3.23 g, 10 mmol) in CH_2Cl_2 (100 ml) at 0 ^{0}C was added boron tribromide (2.84 ml, 30 mmol). After stirring for 1 hour, the mixture was quenched with saturated $NaHCO_3$ solution with ice bath cooling and extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, CH_2Cl_2/MeOH, 40:1 to 20:1) to give **8** (1.68 g, 72% yield) as an off-white solid.

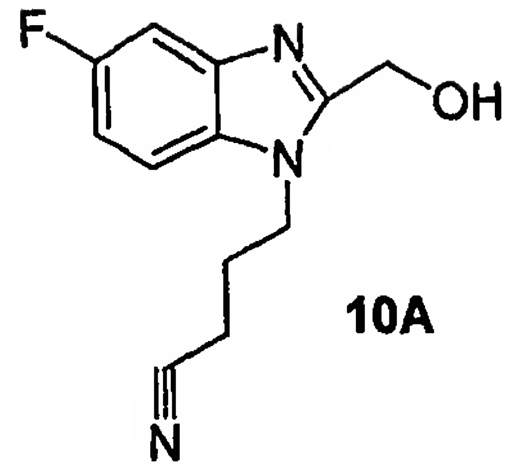
^{1}H NMR ($CDCl_3$) δ 2.25-2.30 (m, 2 H), 2.43 (t, J = 7.1 Hz, 2 H), 4.41 (t, J = 7.1 Hz, 2 H), 4.85 (s, 2 H), 7.04-7.081 (m, 1 H), 7.29-7.34 (m, 2 H);
MS m/e 234 (MH^+).



9

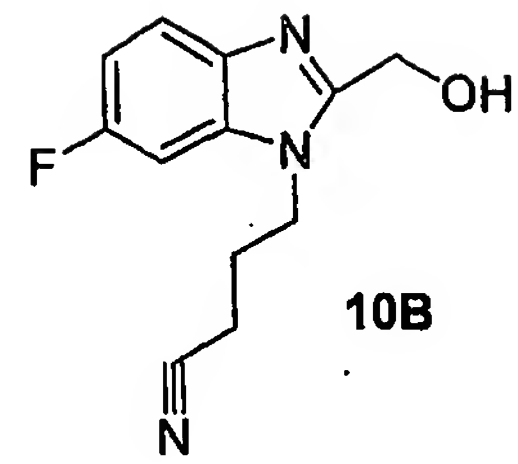
Compound **9** was prepared according to the same procedure described for compound **2**.

^{1}H NMR (CD_3OD) δ 2.30-2.36 (m, 2 H), 2.70 (t, J = 7.2 Hz, 2 H), 4.67 (t, J = 7.6 Hz, 2 H), 5.30 (s, 2 H), 7.49-7.54 (dt, J = 2.4, 9.2 Hz, 1 H), 7.62-7.64 (dd, J = 2.4, 8.0 Hz, 1 H), 8.01-8.04 (dd, J = 2.0, 9.2 Hz, 1 H);
MS m/e 252 (MH^+).



10A

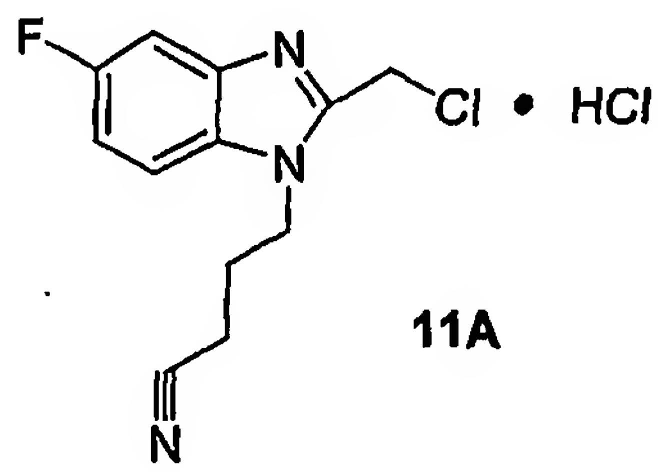
+



10B

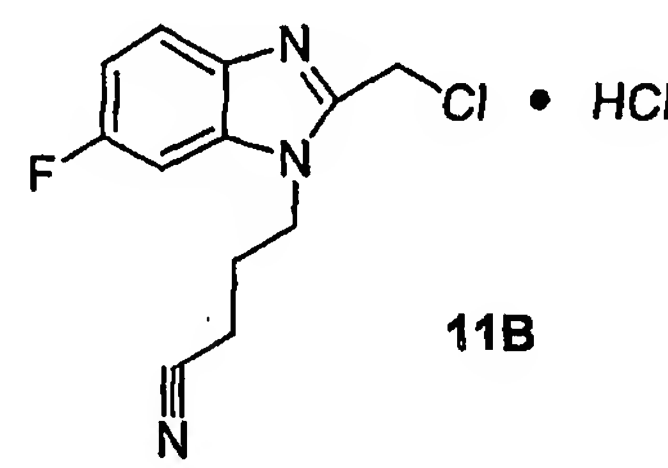
A mixture of **10A** and **10B** was prepared from 5-fluoro-2-hydroxymethyl-benzimidazole using the same procedure described for compound **1**.

^{1}H NMR ($CDCl_3$) δ 2.26-2.30 (m, 2 H), 2.42-2.46 (m, 2 H), 4.36-4.42 (m, 2 H), 4.87 (s, 2 H), 7.03-7.07 (m, 1.5 H), 7.30-7.32 (m, 1 H), 7.60-7.63 (m, 0.5 H); MS m/e 234 (MH^+).



11A

+

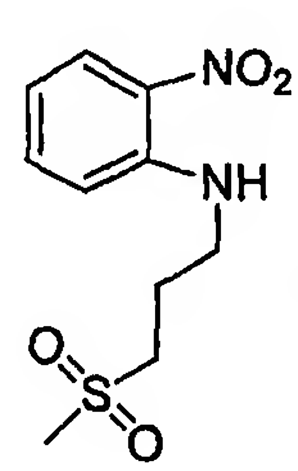


11B

Compounds **11A** and **11B** were prepared according to the same procedure described for compound **2**.

^{1}H NMR ($CDCl_3$) δ 2.24-2.30 (m, 2 H), 2.44-2.47 (m, 2 H), 4.32-4.39 (m, 2 H), 4.829 (s, 1 H), 4.831 (s, 1 H), 7.01-7.11 (m, 1.5 H), 7.30-7.33 (dd, J = 4.4, 8.8 Hz, 0.5 H), 7.40-7.42 (dd, J = 2.3, 9.0 Hz, 0.5 H), 7.66-7.68 (dd, J = 4.8, 8.8 Hz, 0.5 H);

MS m/e 252 (MH^+).

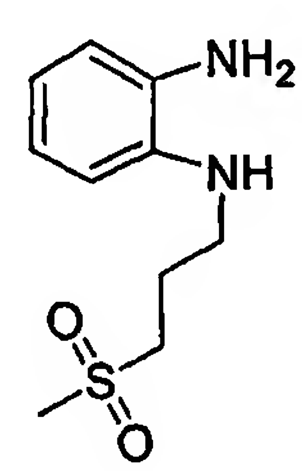


12

2-Fluoronitrobenzene (35.4 g, 250.9 mmol), 3-(methylthio)propylamine (24.0g, 228.1 mmol) and potassium carbonate (47.3 g, 342 mmol) were stirred in CH_3CN (100 mL) at room temperature overnight. After stirring for an additional hour at reflux, the mixture was cooled to room temperature and filtered. The filtrate was evaporated. To the residue in DMF (150 mL), magnesium monoperoxyphthalate hexahydrate (MMPP, 168 g, 340 mmol) was added in several portions with ice-water cooling. The mixture was stirred at room temperature for 3 hours and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with 1 N NaOH, water, brine, dried over $MgSO_4$ and evaporated. The residue was triturated with hot EtOAc to give **12** (48.7 g, 75% yield) as an orange solid.

^{1}H NMR ($CDCl_3$) δ 2.25-2.35 (m, 2 H), 2.97 (s, 3 H), 3.17 (t, J = 7.2 Hz, 2 H), 3.59 (t, J = 6.9 Hz, 2 H), 6.68 -6.74 (m, 1 H), 6.89 (d, J = 8.1 Hz, 1 H), 7.45-7.51 (m, 1 H), 8.20 (dd, J = 1.5, 8.7 Hz, 1 H);
MS m/e 259 (MH^+);

Anal. Calcd for $C_{10}H_{14}N_2O_4S$:	C, 46.50; H, 5.46; N, 10.84
Found:	C, 46.53; H, 5.54; N, 10.90.

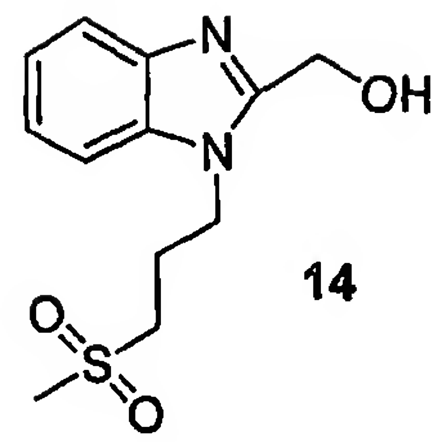


13

To a suspension of **12** (48.5 g, 187.8 mmol) in a mixture of $CHCl_3$ and MeOH (150 mL,1:3) was added 10% palladium on carbon (6 g) under nitrogen. The reduction was carried out in a Parr shaker with hydrogen pressure maintained between 40 and 60 psi for 25 minutes. The catalyst was removed by filtration through a pad of Celite and the filtrate was evaporated to give crude **13**.

^{1}H NMR (CD_3OD) δ 2.11-2.21 (m, 2 H), 2.98 (s, 3 H), 3.28-3.36 (m, 4 H), 6.75 (dt, J = 0.9, 7.2 Hz, 1 H), 6.85 (d, J = 7.5 Hz, 1 H), 7.06-7.12 (m, 2 H);

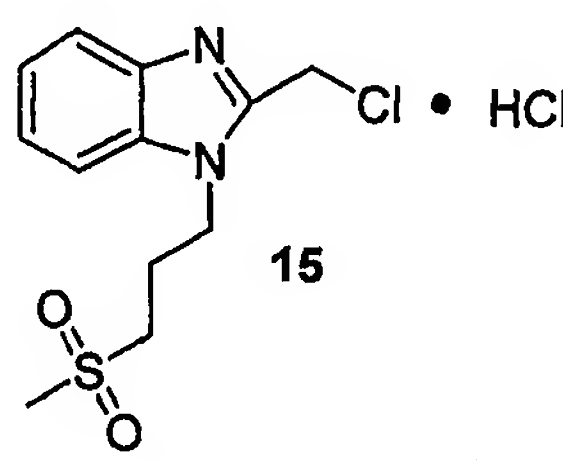
MS m/e 229 (MH^+).



14

The crude diamine **13** obtained above was stirred at reflux overnight with glycolic acid (15.7 g, 207 mmol) in 6 N HCl (150 mL). The solution was cooled in an ice bath and neutralized with concentrated NH_4OH solution, extracted with EtOAc, dried over $MgSO_4$ and evaporated. The residue was purified by chromatography (gradient, EtOAc/hexane, 1:1 to EtOAc/MeOH, 10:1) to give a product which crystallized from EtOAc/MeOH to afford 25.7 g (51% yield in two steps) of **14**.

^{1}H NMR (CD_3OD) δ 2.38-2.44 (m, 2 H), 2.97 (s, 3 H), 3.24 (t, J = 7.6 Hz, 2 H), 4.54 (t, J = 7.6 Hz, 2 H), 7.27 (t, J = 1.1, 8.1 Hz, 1 H), 7.33 (dt, J = 1.1, 8.0 Hz, 1 H), 7.62 (d, J = 8.1 Hz, 1 H), 7.64 (dd, J = 1.0, 8.0 Hz, 1 H);
MS m/e 269 (MH^+).

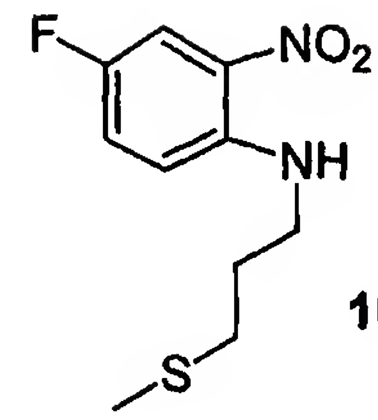


15

Compound **15** was prepared according to the same procedure described for compound **2**.

^{1}H NMR (CD_3OD) δ 2.46-2.52 (m, 2 H), 3.03 (s, 3 H), 3.37 (t, J = 7.1 Hz, 2 H), 4.77 (t, J = 7.8 Hz, 2 H), 5.31 (s, 2 H), 7.68-7.73 (m, 2 H), 7.86 (dd, J = 2.8, 6.9 Hz, 1 H), 8.03 (dd, J = 1.7, 6.1 Hz, 1 H);

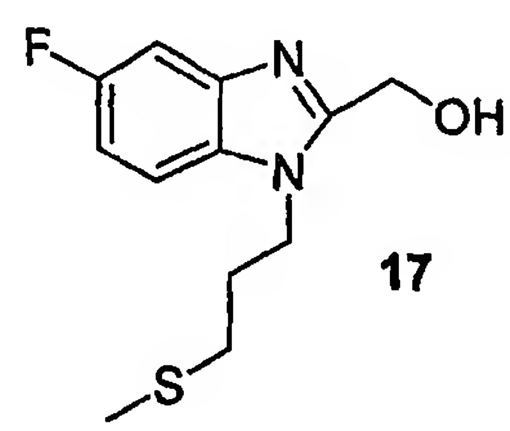
MS m/e 287 (MH^+).



16

To a solution of 2,5-difluoronitrobenzene (15.1 g, 95.06 mmol) in CH_3CN (150 mL) was added potassium carbonate (26.3 g, 190.11 mmol) and 3-(methylthio)propylamine (10.0 g, 95.06 mmol). The mixture was stirred vigorously with the aid of a mechanical stirrer for 16 hours at room temperature. The solid was filtered and the filtrate was evaporated. The residue was diluted with EtOAc (600 mL) and washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to give crude **16** as an orange solid (25 g, 70% pure).

^1H NMR ($CDCl_3$) δ 1.97-2.01 (m, 2 H), 2.11 (s, 3 H), 2.62 (t, J = 6.9 Hz, 2 H), 3.43 (q, J = 6.3 Hz, 2 H), 6.87 (dd, J = 4.6, 9.3 Hz, 1 H), 7.22-7.24 (m, 1 H), 7.85 (dd, J = 3.1, 9.3 Hz, 1 H), 7.95 (bs, 1 H);
MS m/e 245 (MH^+).

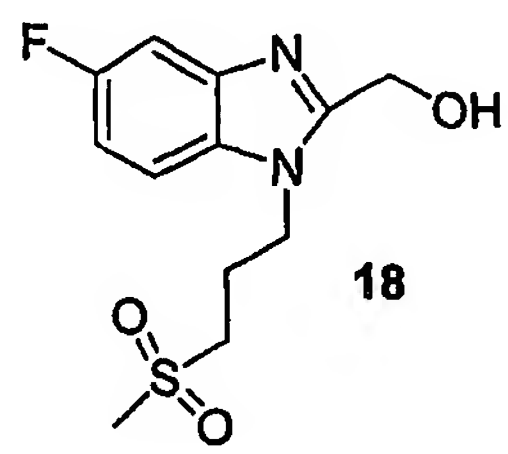


17

A solution of **16** (25 g) in MeOH (300 mL) was added to a mixture of iron powder (12.0 g, 214.9 mmol) and ammonium chloride (19.2 g, 358.2 mmol) in water (100 mL). The reaction mixture was vigorously stirred with a mechanical stirrer and heated at 90 °C for 16 hours. The mixture was filtered through a plug of Celite which was rinsed with hot methanol. The solvent was evaporated to give the crude diamine. LC-MS m/e 215 (MH^+).

The diamine (500 mg crude, 2.33 mmol) and glycolic acid (266 mg, 3.50 mmol) were heated at reflux in 4 N hydrochloric acid (15 mL) for 16 hours. The aqueous solution was cooled and neutralized with concentrated NH_4OH (15 mL). The aqueous solution was then extracted with EtOAc. The organic extracts were dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (gradient, EtOAc/hexanes, 2:1 to EtOAc/MeOH, 10:1) to give **17** (150 mg, 25% yield).

^{1}H NMR (CD_3OD) δ 2.08 (s, 3 H), 2.12-2.20 (m, 2 H), 2.53 (t, J = 6.9 Hz, 2 H), 4.43 (t, J = 6.3 Hz, 2 H), 4.85 (s, 2 H), 7.07 (dt, J = 2.4, 9.2 Hz, 1 H), 7.30 (dd, J = 2.4, 9.3 Hz, 1 H), 7.53 (dd, J = 4.6, 8.9 Hz, 1 H);
MS m/e 255 (MH^+).



18

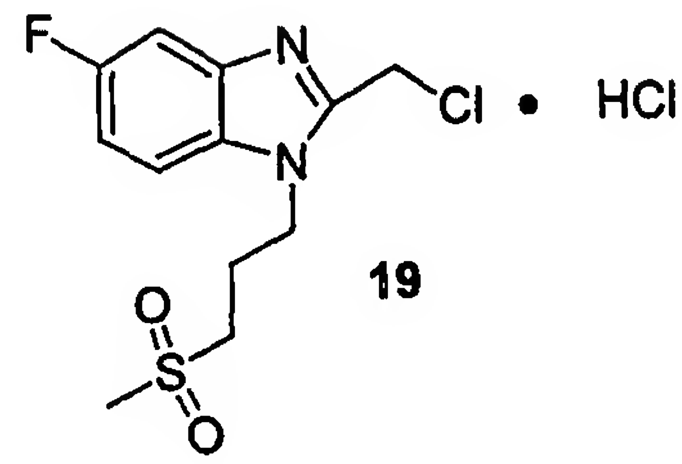
To a solution of sulfide **17** (150 mg, 0.59 mmol) in DMF (5 mL) was added magnesium monoperoxyphthate hexahydrate (MMPP, 583 mg, 1.18 mmol). The reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated, and the residue was diluted with water and extracted with EtOAc. The combined extracts were washed with saturated aqueous sodium bicarbonate solution and dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (gradient, straight EtOAc to EtOAc/MeOH, 10:1) to give **18** (129 mg, 76% yield) as a white solid.

^{1}H NMR (CD_3OD) δ 2.37-2.47 (m, 2 H), 3.00 (s, 3 H), 3.26 (t, J = 7.4 Hz, 2 H), 4.55 (t, J = 7.5 Hz, 2 H), 7.14 (dt, J = 2.4, 9.4 Hz, 1 H), 7.34 (dd, J = 2.4, 9.2 Hz, 1 H), 7.62 (dd, J = 4.5, 8.9 Hz, 1 H);
IR (KBr, cm^{-1}) 3139, 1624, 1591, 1489, 1478, 1446, 1416, 1308, 1270, 1143, 1134, 1047, 951, 859, 802, 527, 500;

MS m/e 287 (MH^+);

Anal. Calcd for $C_{12}H_{15}FN_2O_3S$: C, 50.33; H, 5.28; N, 9.78

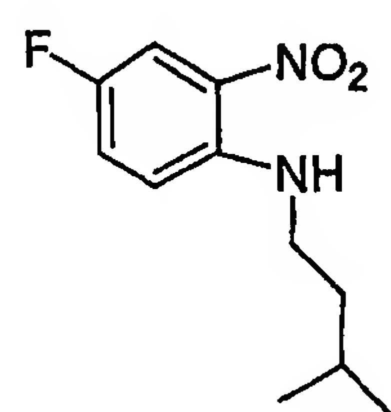
Found: C, 50.17; H, 5.17; N, 9.57.



19

Compound **19** was prepared according to the same procedure described for compound **2**.

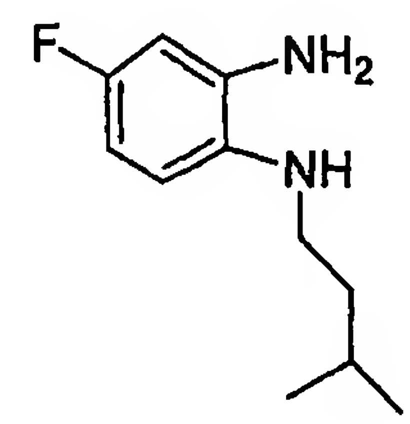
^{1}H NMR (DMSO-d_6) δ 2.15-2.20 (m, 2 H), 3.00 (s, 3 H), 3.26 (t, J = 7.2 Hz, 2 H), 4.47 (t, J = 7.8 Hz, 2 H), 5.11 (s, 2 H), 7.27 (dt, J = 2.4, 9.4 Hz, 1 H), 7.51 (dd, J = 2.4, 9.0Hz, 1 H), 7.76 (dd, J = 4.8, 9.0 Hz, 1 H);
IR (KBr, cm^{-1}) 3429, 2577, 1635, 1536, 1496, 1290, 1277, 1130, 962, 927, 784;
MS m/e 305 (MH^+).



20

To a solution of 2,5-difluoronitrobenzene (45 g, 282.86 mmol) in CH_3CN (500 mL) was added potassium carbonate (78 g, 565.72 mmol) and isoamylamine (25 g, 282.86 mmol). The reaction mixture was stirred at room temperature for 18 hours with the aid of a mechanical stirrer. The potassium carbonate was filtered and the filtrate was evaporated to give an orange oil. The oil was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by flash column chromatography (hexanes/EtOAc, 20:1) gave 53 g (83% yield) of compound **20**.

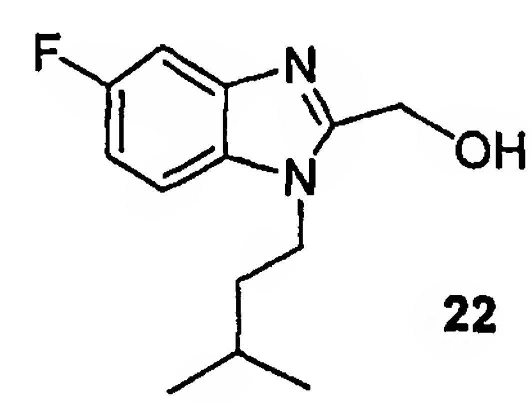
^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 6.5 Hz, 6 H), 1.61-1.65 (m, 2 H), 1.74-1.78 (m, 1 H), 3.30 (t, J = 7.3 Hz, 2 H), 6.83 (dd, J = 4.6, 9.5 Hz, 1 H), 7.23-7.27 (m, 1 H), 7.85 (dd, J = 3.1, 9.2 Hz, 1 H).



21

To a solution of compound **20** (53 g, 235.14 mmol) and concentrated HCl (15 mL) in MeOH (200 mL) was added 10% palladium on carbon (5 g) and the mixture was agitated under H_2 at 55 psi for 1.5 hours. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give 47 g (87% yield) of diamine **21** as the HCl salt.

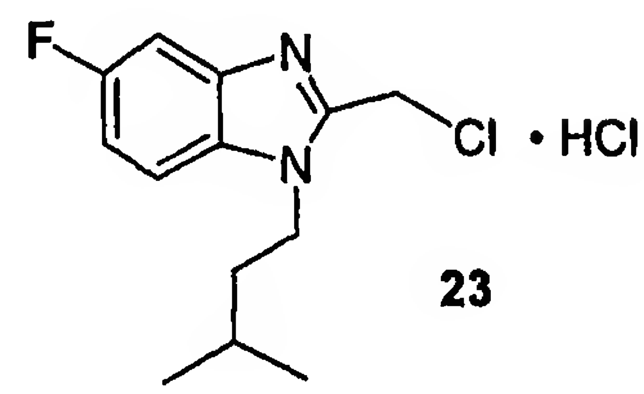
^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.2 Hz, 6 H), 1.65-1.77 (m, 3 H), 3.36 (t, J = 8.0 Hz, 2 H), 6.50-6.57 (m, 1 H), 6.71 (dd, J = 2.7, 10.5 Hz, 1 H), 7.28 (dd, J = 5.5, 8.8 Hz, 1 H);
MS m/e 197 (MH^+).



22

A mixture of diamine **21** (47 g, 200.66 mmol) and glycolic acid (16 g, 210.70 mmol) in 4 N HCl (500 mL) was stirred at reflux for 18 hours. The reaction mixture was cooled first to room temperature and then to 0 °C. The reaction was diluted with concentrated ammonium hydroxide (200 mL) until the pH was adjusted to approximately 8. The product was extracted with EtOAc, dried over $MgSO_4$, and evaporated. The crude product was recrystallized with EtOAc/hexanes to give 27 g (37% yield) of compound **22** as brown crystals.

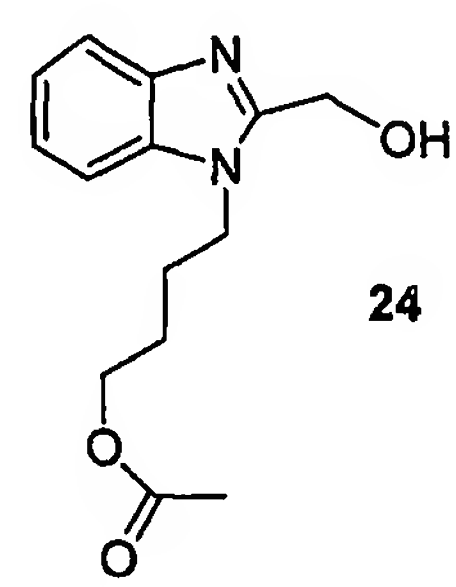
^{1}H NMR ($CDCl_3$) δ 1.02 (d, J = 6.0 Hz, 6 H), 1.68-1.75 (m, 3 H), 3.19 (bs, 1 H), 4.22 (t, J = 7.7 Hz, 2 H), 4.93 (s, 2 H), 7.06 (dt, J = 2.2, 9.1 Hz, 1 H), 7.26-7.28 (m, 1 H), 7.37 (dd, J = 2.1, 8.9 Hz, 1 H);
MS m/e 237 (MH^+).



23

Compound **23** was prepared according to the same procedure described for compound **2.**

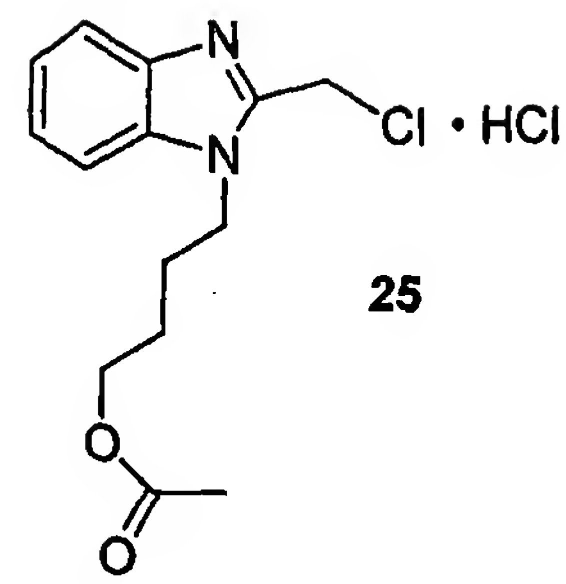
^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 6.4 Hz, 6 H), 1.79-1.90 (m, 3 H), 4.44 (bt, J = 8.2 Hz, 2 H), 5.32 (s, 2 H), 7.36 (dt, J = 2.2, 8.9, 1 H), 7.54-7.59 (m, 2 H);
MS m/e 255 (MH^+).



24

Compound **24** was prepared using the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with 4-bromobutyl acetate.

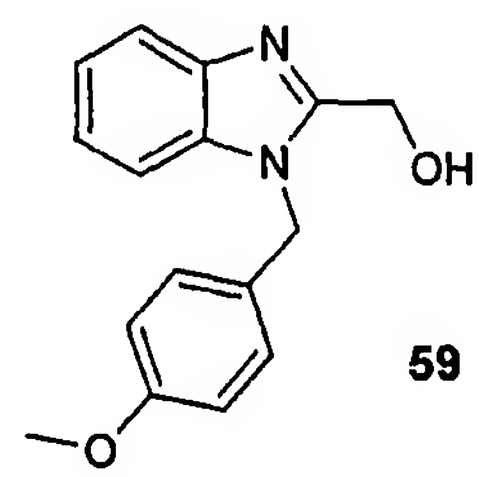
^{1}H NMR ($CDCl_3$) δ 1.68-1.72 (m, 2 H), 1.91-1.94 (m, 2 H), 2.03 (s, 3 H), 4.07 (t, J = 6.4 Hz, 2 H), 4.26 (t, J = 7.5 Hz, 2 H), 4.86 (s, 2 H), 6.86 (bs, 1 H), 7.20-7.29 (m, 3 H), 7.65 (dd, J = 1.8, 6.7 Hz, 1 H);
MS m/e 263 (MH^+).



25

Compound **25** was prepared according to the same procedure described for compound **2**.

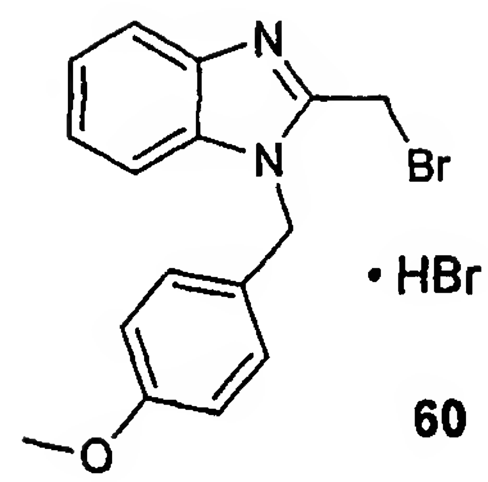
^{1}H NMR ($CDCl_3$) δ 1.80-1.86 (m, 2 H), 2.03 (s, 3 H), 2.06-2.12 (m, 2 H), 4.14 (t, J = 6.1 Hz, 2 H), 4.55 (t, J = 8.1 Hz, 2 H), 5.42 (s, 2 H), 7.48 (t, J = 7.3 Hz, 1 H), 7.55 (t, J = 7.3 Hz, 1 H), 7.64 (d, J = 8.5 Hz, 1 H), 7.78 (d, J = 8.2 Hz, 1 H); MS m/e 281 (MH^+).



59

Compound **59** was prepared using the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with 4-methoxybenzyl chloride.

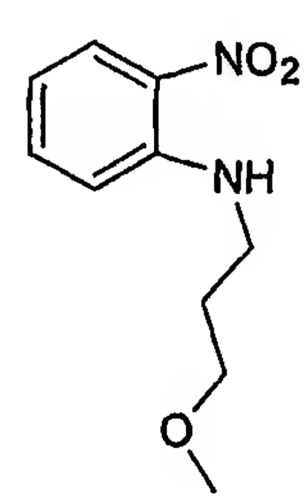
^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3 H), 4.99 (s, 2 H), 5.45 (s, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 7.11 (d, J = 8.6 Hz, 2 H), 7.28-7.34 (m, 3 H), 7.75 (d, J = 6.8, 1 H); MS m/e 269 (MH^+).



60

Compound **59** (4,75 g, 17.7 mmol) was combined with CH_2Cl_2 (100 mL) and the mixture was treated with (bromomethylene)dimethylammonium bromide (5.25 g, 23.0 mmol). The reaction was stirred at room temperature for 30 minutes and then filtered to isolate a white solid. The solid was rinsed with CH_2Cl_2, then with diethyl ether. The solid was triturated with water (50 mL), isolated by filtration, rinsed with water, then with acetone, and finally with Et_2O. The white powder was labeled crop 1 and set aside. All liquids were combined and concentrated in vacuo to give an off-white solid which was triturated with a mixture of acetone (50 mL) and Et_2O (300 mL). The liquid was decanted and the solid was suspended in acetone and isolated by filtration to give crop 2. Crops 1 and 2 were determined to be spectroscopically identical and were combined to give 6.65 g (91 % yield) of compound **60** as a white powder.

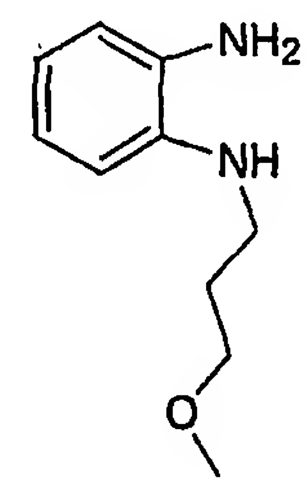
^{1}H NMR (DMSO-d_6) δ 3.72 (s, 3 H), 5.18 (s, 2 H), 5.68 (s, 2 H), 6.92 (d, J = 8.7 Hz, 2 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 7.44-7.47 (m, 2 H), 7.62-7.63 (m, 1 H), 7.78-7.80 (m, 1 H);
MS m/e 332 (MH^+).



61

Compound **61** was prepared according to the same procedure described for compound **16** using 3-methoxypropylamine instead of 3-(methylthio)propylamine.

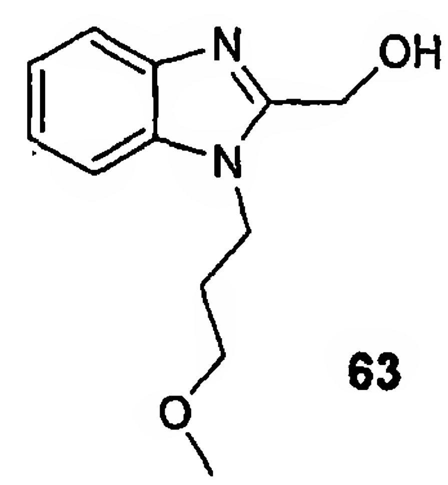
^{1}H NMR ($CDCl_3$) δ 1.95-2.00 (m, 2 H), 3.37 (s, 3 H), 3.39-3.43 (m, 2 H), 3.52 (t, *J* = 5.7 Hz, 2 H), 6.61 (t, *J* = 8.2 Hz, 1 H), 6.86 (d, *J* = 8.8 Hz, 1 H), 7.41 (t, *J* = 7.9 Hz, 1 H), 8.14 (dd, J = 1.4, 8.7 Hz, 1 H), 8.26 (bs, 1 H);
MS m/e 211 (MH^+).



62

Compound **62** was prepared from compound **61** according to the same procedure described for compound **13** and was used immediately upon isolation.

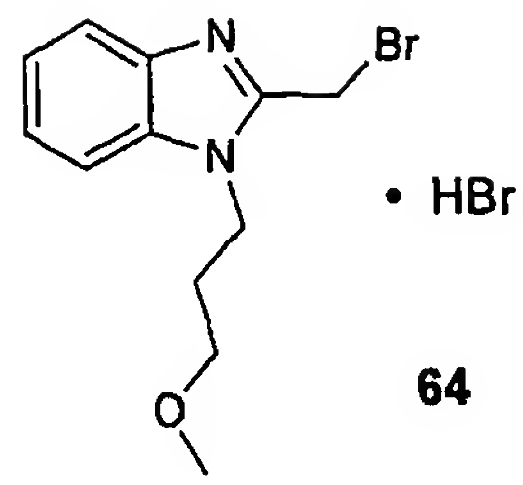
MS m/e 181 (MH^+).



63

Compound **63** was prepared from compound **62** according to the same procedure described for compound **14.**

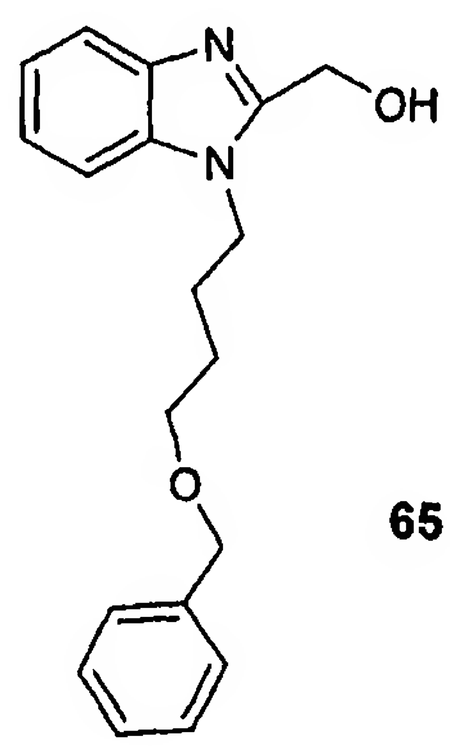
^{1}H NMR ($CDCl_3$) δ 2.09-2.14 (m, 2 H), 3.30 (t, J = 5.7 Hz, 2 H), 3.33 (s, 3 H), 4.35 (t, J = 6.9 Hz, 2 H), 4.89 (s, 2 H), 7.22-7.26 (m, 2 H), 7.35-7.37 (m, 1 H), 7.69-7.70 (m, 1 H);
MS m/e 221 (MH^+).



64

A solution of compound **63** (1.50 g, 6.81mmol) in CH_3CN (20 mL) was treated with (bromomethylene)dimethylammonium bromide. The reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched with H_2O (3 mL) and the solvent was evaporated and dried under vacuum to give compound **64** which was used immediately upon isolation.

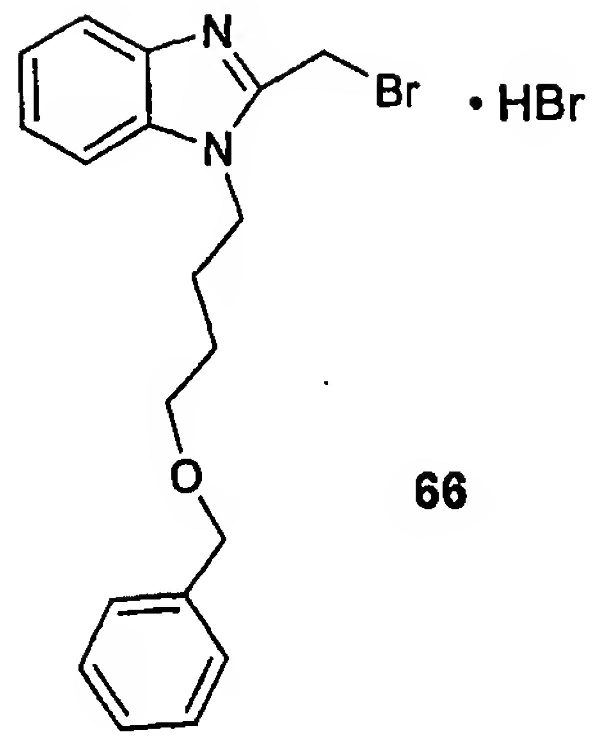
MS m/e 283, 285 (MH^+).



65

Compound **65** was prepared according to the same procedure described for compound **1**, except that 4-bromobutyronitrile was replaced with benzyl 4-bromobutylether.

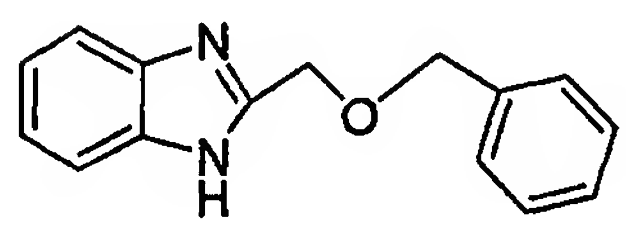
^{1}H NMR (CD_3OD) δ 1.65-1.71 (m, 2 H), 1.94-1.99 (m, 2 H), 3.52 (t, J = 6.2 Hz, 2 H), 4.36 (t, J = 7.7 Hz, 2 H), 4.47 (s, 2 H), 4.84 (s, 2 H), 7.22-7.27 (m, 3 H), 7.27-7.31 (m, 4 H), 7.48 (d, J = 7.4 Hz, 1 H), 7.61 (dd, J = 1.4, 7.1 Hz, 1 H);
MS m/e 311 (MH^+).



66

Compound **66** was prepared according to the same procedure described for compound **64**.

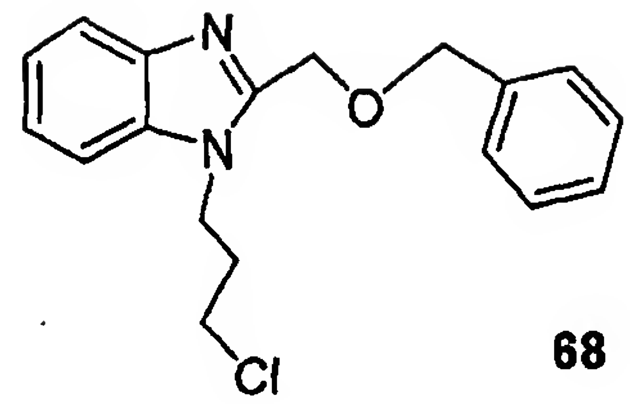
MS m/e 373, 375 (MH^+).



67

To a suspension of 1,2-phenylenediamine (50 g, 462 mmol) in THF (150 mL) cooled at 0°C was slowly added a solution of benzyloxyacetyl chloride (171 g, 924 mmol) in THF (100 mL). The reaction mixture was stirred for 3 hours. The reaction mixture was cooled to 0 °C with an ice bath and 4N HCl (300 mL) was slowly added to the reaction mixture. The ice bath was removed and the mixture was heated at reflux for 18 hours. The majority of the THF was evaporated. The aqueous material was neutralized with 10 N NaOH, extracted with EtOAc, dried over $MgSO_4$, and evaporated to give a tan solid. The solid was recrystallized from EtOAc to give 45 g (41% yield) of compound **67**.

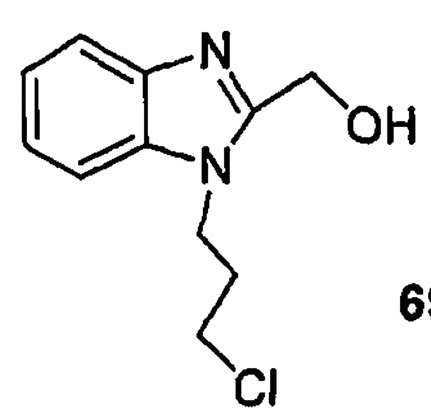
^1H NMR (CD_3OD) δ 4.65 (s, 2 H), 4.77 (s, 2 H), 7.22-7.41 (m, 7 H), 7.56 (dd, J = 3.2, 6.1 Hz, 2 H);
MS m/e 239 (MH^+).



68

To a solution of compound **67** (6.00 g, 25.18 mmol) in DMF (50 mL) was added sodium hydride (60% dispersion in mineral oil, 1.46 g, 36.52 mmol). The reaction mixture was cooled to 0 °C and stirred for 30 minutes. To the cooled mixture 1-bromo-3-chloropropane (5.35 g, 32.99 mmol) was added and the reaction mixture was stirred for 4.5 hours. The mixture was diluted with H_2O (75 mL) and extracted with Et_2O (3 x 300 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. Purification by flash column chromatography on silica (gradient, hexanes/EtOAc 2:1 to 1:1) gave 6.86 g (87% yield) of compound **68**.

^{1}H NMR ($CDCl_3$) δ 2.22-2.36 (m, 2 H), 3.53 (t, J = 6.0 Hz, 2 H), 4.45 (t, J = 7.0 Hz, 2 H), 4.62 (s, 2 H), 4.90 (s, 2 H), 7.28-7.44 (m, 7 H), 7.42-7.48 (m, 1 H), 7.79-7.82 (m, 1 H);
MS m/e 315, 317 (MH^+).

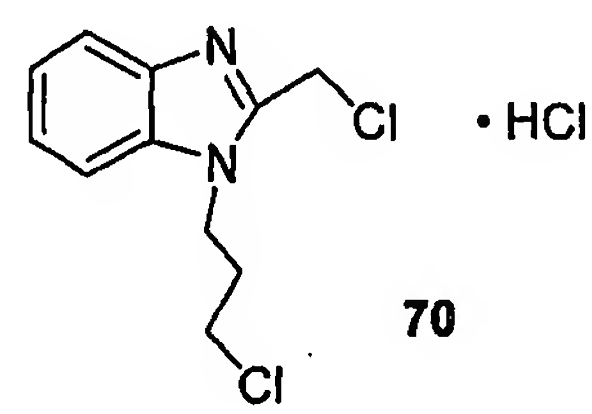


69

A solution of compound **68** (4.00 g, 12.71 mmol) in CH_2Cl_2 (75 mL) was cooled to 0 °C with an ice bath. To this solution was added boron tribromide (0.99M in CH_2Cl_2, 20 mL, 19.76 mmol) slowly via syringe. The reaction mixture was stirred at 0 °C for 2 hours. The reaction was quenched at 0 °C with MeOH (75 mL). The solvent was evaporated with a room temperature rotary evaporator bath. More MeOH was added and was again evaporated. The resulting solid was dried under high vacuum for 48 hours to give 3.70 g (95% yield) of compound **69**.

^1H NMR (CD_3OD) δ 2.39-2.44 (m, 2 H), 3.72 (t, J = 6.0 Hz, 2 H), 4.61 (t, J = 7.2 Hz, 2 H), 5.19 (s, 2 H), 7.62-7.68 (m, 2 H), 7.80-7.82 (m, 1 H), 7.93-7.95 (m, 1 H);

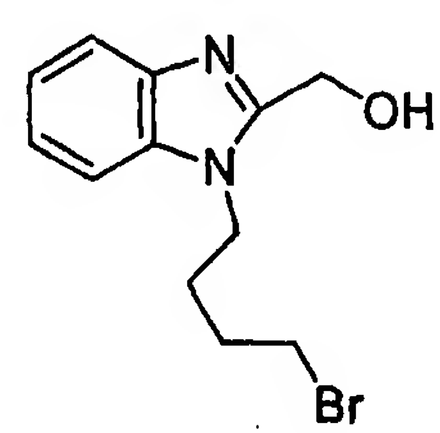
MS m/e 225, 227 (MH^+).



70

Compound **70** was prepared according to the same procedure described for compound **2**.

MS m/e 244 (MH^+).

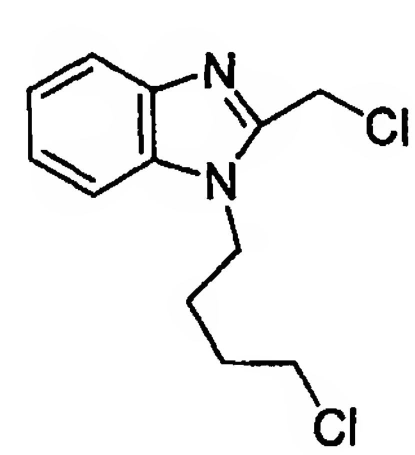


71

Compound **71** was prepared according to the same procedure described for compound **1** using 1,4-dibromobutane and the reaction was carried out at 0 °C.

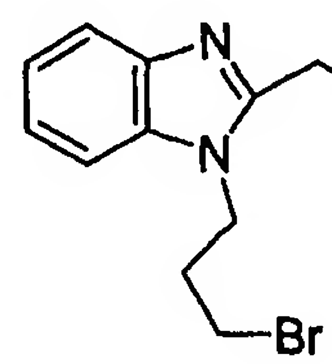
^1H NMR (CD_3OD) δ 1.91-1.95 (m, 2 H), 2.01-2.08 (m, 2 H), 3.48 (t, J=6.6 Hz, 2 H), 4.38 (t, J=7.4 Hz, 2 H), 4.86 (s, 2 H), 7.23-7.27 (m, 1 H), 7.29-7.32 (m, 1H), 7.54 (d, J=8.0 Hz, 1 H), 7.62 (d, J=8.0 Hz, 1 H);

MS m/e 282, 284 (MH^+).



72

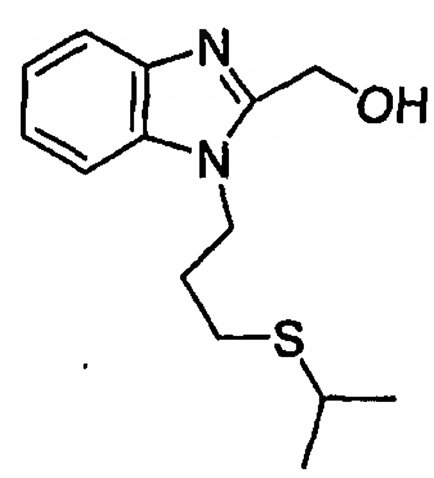
Compound **72** was prepared according to the same procedure described for compound **2** and was used immediately upon isolation.



73

Compound **73** was prepared according to the same procedure described for compound **1** using 1,3 dibromopropane and the reaction was carried out at 0 °C.

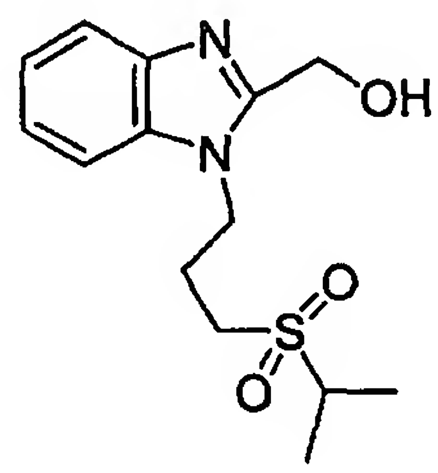
^{1}H NMR ($CDCl_3$) δ 2.42-2.47 (m, 2 H), 3.43 (t, J= 6.1 Hz, 2 H), 4.43 (t, J=7.0 Hz, 2 H), 4.94 (s, 2 H), 7.25-7.32 (m, 2 H), 7.42-7.44 (m, 1 H), 7.68-7.70 (m, 1 H); MS m/e 268, 270 (MH^+).



74

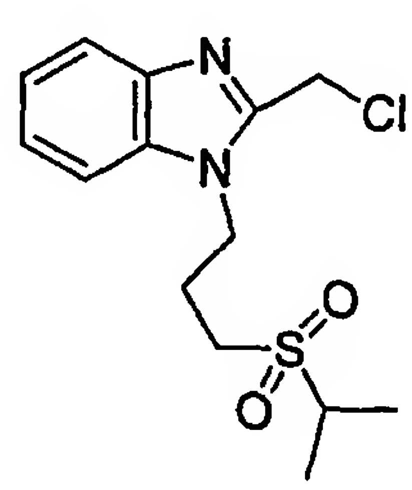
2-Propanethiol (305 mg, 4.00 mmol) and sodium hydride (60% dispersion in mineral oil, 240 mg, 6.00 mmol) were stirred together in DMF (20 mL) and then cooled to 0 °C. To this mixture was added compound **73** (542 mg, 2.00 mmol) and the reaction mixture was allowed to warm to room temperature over 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by column chromatography (gradient, CH_2Cl_2/MeOH, 40:1 to 20:1) gave 310 mg (59% yield) of compound **74** as an off-white oil.

^{1}H NMR (CD_3OD) δ 1.22 (d, J = 6.7 Hz, 6 H), 2.10-2.18 (m, 2 H), 2.58 (t, J=7.0 Hz, 2 H), 2.90-2.93 (m, 1 H), 4.45 (t, J=7.3 Hz, 2 H), 4.87 (s, 2 H), 7.23-7.32 (m, 2 H), 7.55 (d, J=8.0 Hz, 1 H), 7.62 (d, J=7.9 Hz, 1 H);
MS m/e 265 (MH^+).

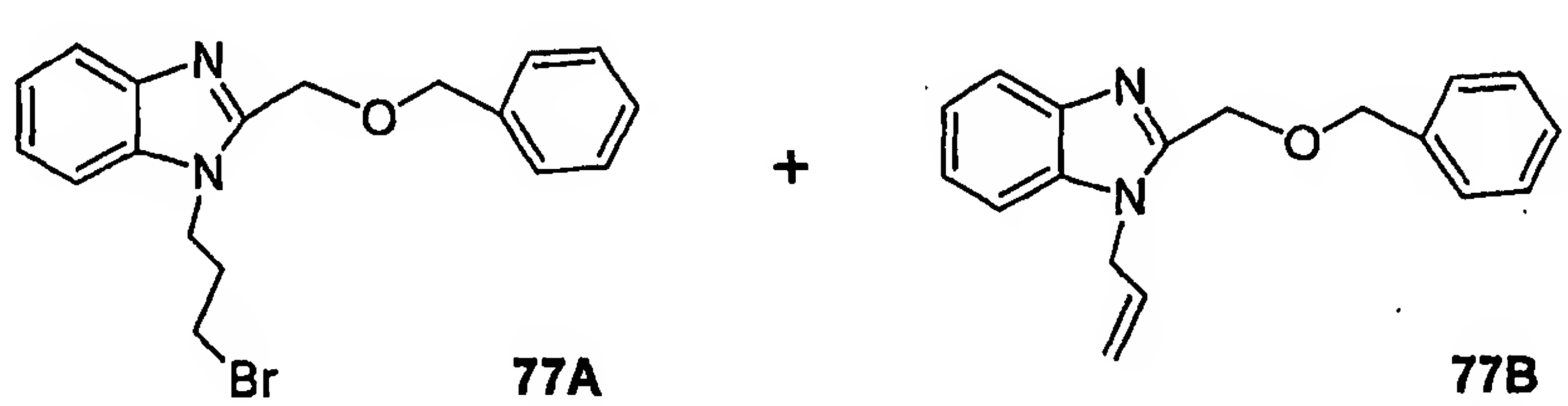

75

Compound **75** was prepared from compound **74** according to the same procedure described for compound **18**.

^{1}H NMR (CD_3Cl) δ 1.32-1.36 (m, 6 H), 2.44-2.50 (m, 2 H), 3.00-3.02 (m, 2 H), 3.06-3.10 (m, 1 H), 4.48 (t, J=7.3 Hz, 2 H), 4.87 (s, 2 H), 7.23-7.30 (m, 2 H), 7.42 (d, J=7.7 Hz, 1 H), 7.65 (d, J=7.8 Hz, 1 H);
MS m/e 297 (MH^+).

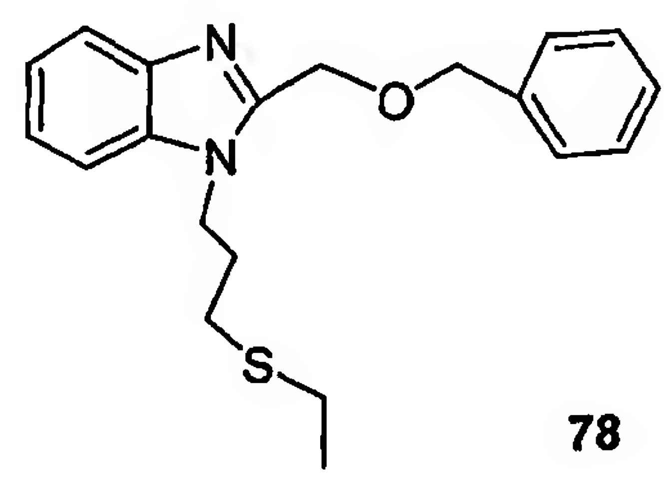

76

Compound **76** was prepared according to the same procedure described for compound **2** and was used immediately upon isolation.


77A **77B**

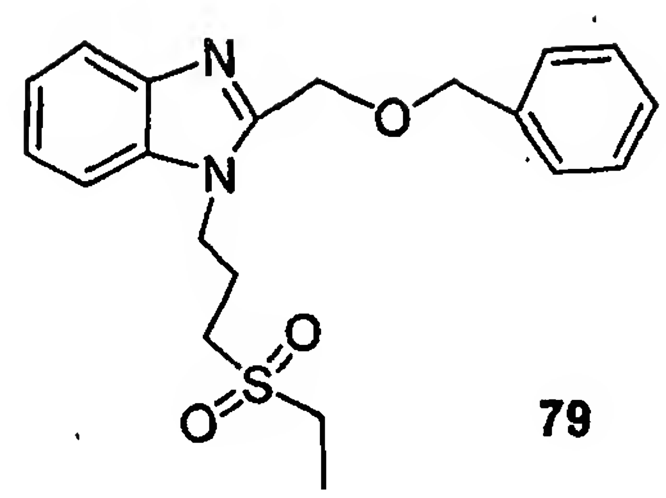
To a solution of compound **67** (18.25 g, 76.59 mmol) in DMF (85 mL) was added sodium hydride (60% dispersion in mineral oil, 3.37 g, 84.25 mmol). The reaction mixture was stirred for 30 minutes and then cooled to 0 °C. 1,3-Dibromopropane was slowly added to the cooled solution. The temperature was raised to room temperature after 20 minutes as no starting material remained. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and evaporated. Column chromatography (hexanes/EtOAc, 2:1) gave 5.2 g of a 60/40 mixture of the desired bromide compound **77A** (8% yield) and an undesired elimination product **77B**. This mixture was used in the next step without further purification.

Bromide **77A** : MS m/e 360,361 (MH^+);
Elimination product **77B** : MS m/e 279 (MH^+).



78

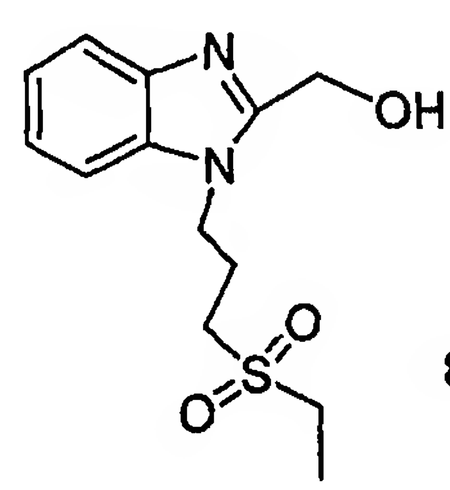
To a solution of ethanethiol (1.04 g, 16.77 mmol) in DMF (60 mL) was added sodium hydride (60% dispersion in mineral oil, 670 mg, 16.77 mmol). The mixture was stirred for 15 minutes at room temperature and then cooled to 0 °C. In a separate flask, the mixture containing compounds **77A** and **77B** (5.2 g mixture, 3.0 g, 8.38 mmol) was dissolved in DMF (10 mL), cooled to 0 °C and added slowly to the ethanethiol mixture. The reaction mixture was stirred for 1 hour while the temperature was slowly allowed to rise to room temperature. The DMF was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$ and evaporated. This material containing compound **78** was used immediately as a mixture without further purification.



79

Compound **79** was prepared from crude **78** according to the same procedure as compound **18** and was purified by flash column chromatography on silica (gradient, EtOAc/hexanes, 2:1 to straight EtOAc).

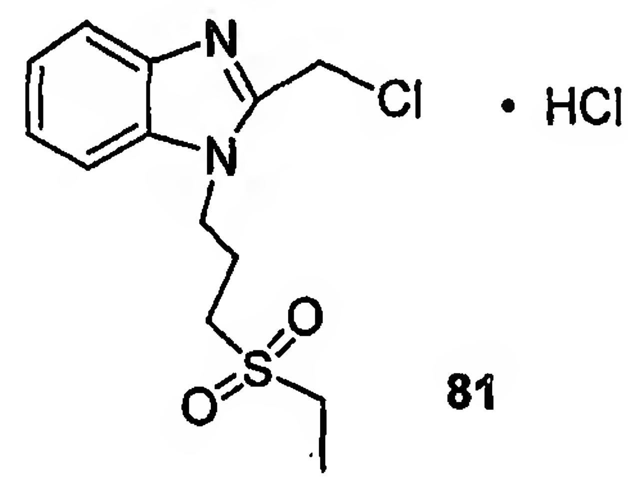
^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.5 Hz, 3 H), 2.35-2.42 (m, 2 H), 2.73 (q, J = 7.5 Hz, 2 H), 2.84-2.88 (m, 2 H), 4.43 (t, J = 7.2 Hz, 2 H), 4.60 (s, 2 H), 4.87 (s, 2 H), 7.27-7.34 (m, 5 H), 7.42 (dd, J = 1.5, 7.0 Hz, 1 H), 7.77 (dd, J = 1.6, 6.9 Hz, 1 H), 8.00 (s, 2 H);
MS m/e 373 (MH^+).



80

A solution of compound **79** (1.95 g, 5.24 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C with an ice bath. To this solution was added boron tribromide (0.99 M in CH_2Cl_2, 9.0 mL, 9.00 mmol) slowly via syringe. The reaction mixture was stirred for 40 minutes at 0 °C before quenching at 0°C by cautious addition of anhydrous MeOH (50 mL). The solvent was evaporated with a room temperature rotary evaporator bath. More anhydrous MeOH was added and the solvent was again evaporated. The resulting solid was dried under high vacuum for 48 hours to give 1.82 g (96% yield) of compound **80**.

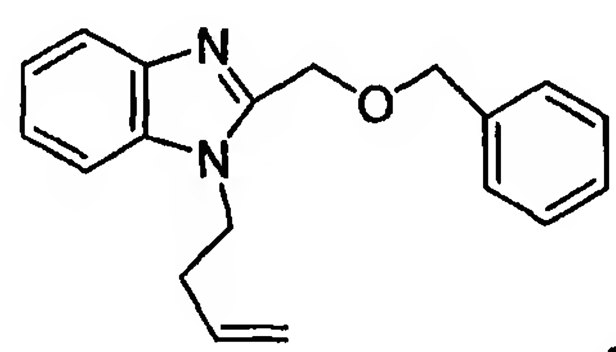
^{1}H NMR (DMSO-d_6) δ 1.22 (t, J = 7.4 Hz, 3 H), 2.23-2.89 (m, 2 H), 3.11 (q, J = 7.4 Hz, 2 H), 3.29 (t, J = 7.7 Hz, 2 H), 4.53 (t, J = 7.5 Hz, 2 H), 5.08 (s, 2 H), 7.58-7.65 (m, 2 H), 7.80 (dd, J = 1.0, 7.3 Hz, 1 H), 8.04 (d, J = 7.75 Hz, 1 H); MS m/e 283 (MH^+).



81

Compound **81** was prepared according to the same procedure described for compound **2**.

MS m/e 301 (MH^+).

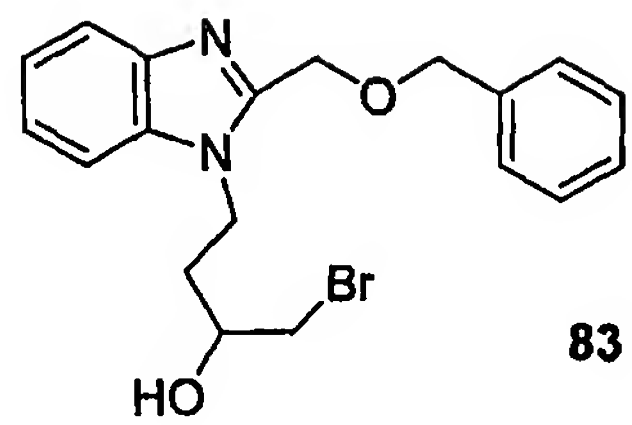


82

To a solution of compound **67** (1.43 g, 6.00 mmol) in DMF (25 mL) was added sodium hydride (60% dispersion in mineral oil, 260 mg, 6.60 mmol) and the mixture was cooled to 0 °C. To the mixture was added 4-bromo-1-butene (972 mg, 7.20 mmol) and the mixture was allowed to stir at room temperature for 18 hours. The reaction mixture was quenched with H_2O and extracted with EtOAc. The organic extracts were washed with water and then brine, dried over $MgSO_4$, and evaporated. Flash column chromatography (gradient, hexanes /EtOAc, 4:1 to 1:1) gave 580 mg (33% yield) of compound **82** as a viscous oil.

^{1}H NMR ($CDCl_3$) δ 2.55-2.59 (m, 2 H), 4.31 (t, J=7.5 Hz, 2 H), 4.59 (s, 2 H), 4.88 (s, 2 H), 5.01 (d, J=7.8 Hz, 1 H), 5.04 (d, J=10.4 Hz, 1 H), 5.71-5.80 (m, 1 H), 7.26-7.39 (m, 8 H), 7.79 (d, J=7.6 Hz, 1 H);

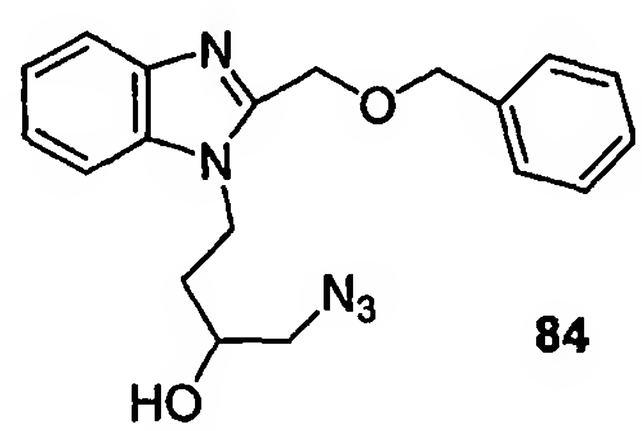
MS m/e 293 (MH^+).



83

To a solution of compound **82** (468 mg, 1.92 mmol) and water (71 mg, 3.93 mmol) in DMSO (5 mL) was added N-bromosuccinimide (NBS, 700 mg, 3.93 mmol) at room temperature and the mixture was stirred for 1 hour. The resulting solution was diluted with EtOAc and washed with H_2O. The organic extracts were dried with $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, hexane:EtOAc 3:1 to 1:2) to give 214 mg (56% yield) of compound **83** as a off-white viscous oil.

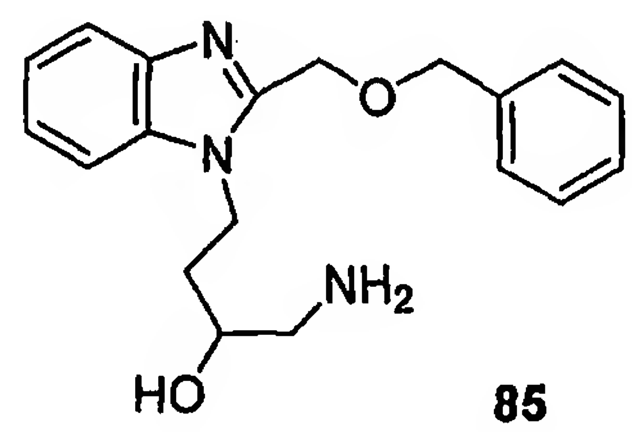
^{1}H NMR ($CDCl_3$) δ 1.90-1.97 (m, 1 H), 2.12-2.18 (m, 1 H), 3.22-3.30 (m, 2 H), 3.61-3.66 (m, 1 H), 4.38-4.50 (m, 2 H), 4.59-4.64 (m, 2 H), 4.87-4.92 (m, 2 H), 7.28-7.37 (m, 7 H), 7.42-7.46 (m, 1 H), 7.78-7.80 (m, 1 H);
MS m/e 389, 391 (MH^+).



84

A mixture of compound **83** (214 mg, 0.55 mmol) and sodium azide (107 mg, 1.65 mmol) in DMF (5 mL) was stirred at 50 °C for 1 hour. The resulting solution was diluted with EtOAc and washed with water. The organic extracts were dried with $MgSO_4$ and evaporated to give 190 mg (98% yield) of compound **84** as a off-white viscous oil.

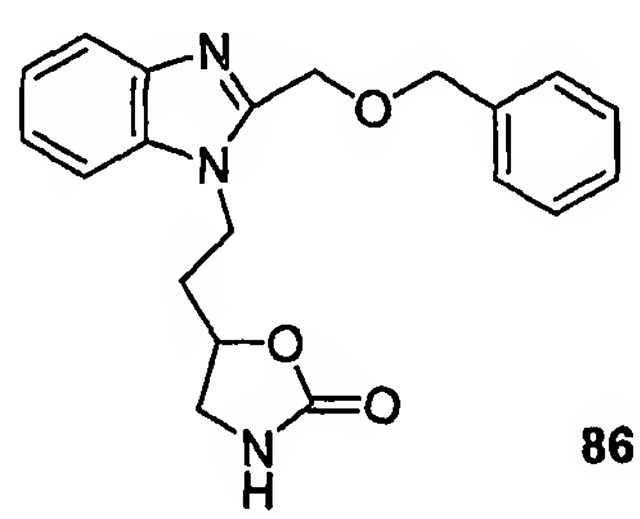
^{1}H NMR ($CDCl_3$) δ 1.84-1.91 (m, 1 H), 2.02-2.09 (m, 1 H), 3.08-3.14 (m, 2 H), 3.52-3.56 (m, 1 H), 4.36-4.41 (m, 1 H), 4.44-4.50 (m, 1 H), 4.60-4.67 (m, 2 H), 4.88-4.93 (m, 2 H), 7.26-7.38 (m, 7 H), 7.42-7.44 (m, 1 H), 7.79-7.81 (m, 1 H); MS m/e 352 (MH^+).



85

Compound **85** was prepared from compound **84** according to the same reduction procedure described for compound **13**.

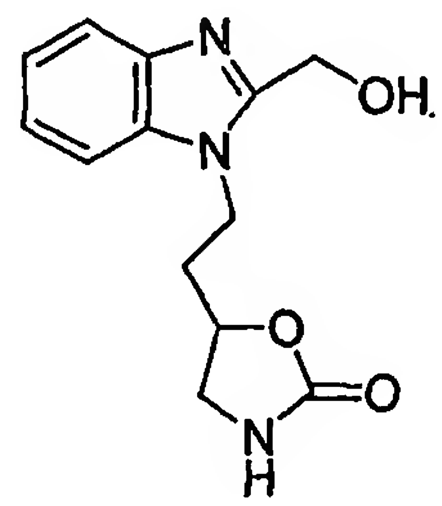
^{1}H NMR (CD_3OD) δ 1.86-1.94 (m, 1 H), 2.03-2.10 (m, 1 H), 2.70-2.74 (m, J=3.2, 12.8 Hz, 1 H), 2.84-2.88 (dd, J=3.2, 12.8 Hz, 1 H), 3.70-3.75 (m, 1 H), 4.44-4.54 (m, 2 H), 4.60-4.65 (m, 2 H), 4.88-4.93 (m, 2 H), 7.27-7.38 (m, 7 H), 7.59 (d, J=8.0 Hz, 1 H), 7.65 (d, J=8.0 Hz, 1 H);
MS m/e 326 (MH^+).



86

A solution of compound **85** (162 mg, 0.50 mmol), carbonyldiimidazole (89 mg, 0.55 mmol) and pyridine (198 mg, 2.50 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 2 hours. The mixture was diluted with CH_2Cl_2 and washed with water. The organic extracts were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, CH_2Cl_2:MeOH, 40:1 to 20:1) to give 130 mg (74% yield) of compound **86** as a off-white viscous oil.

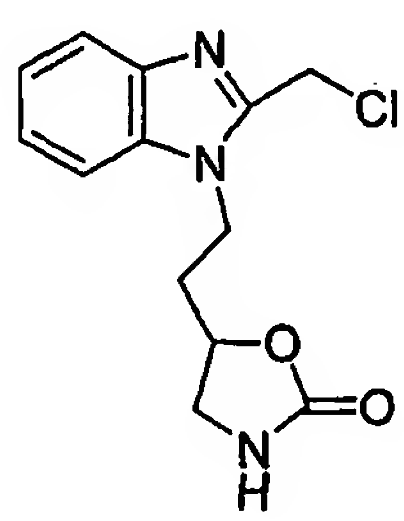
^1H NMR (CD_3OD) δ 2.16-2.21 (m, 2 H), 3.06-3.09 (m, 1 H), 3.52-3.59 (m, 1 H), 4.41-4.50 (m, 2 H), 4.58-4.65 (m, 3 H), 4.80-4.84 (m, 2 H), 7.26-7.38 (m, 6 H), 7.55-7.58 (m, 1 H), 7.82-7.85 (m, 1 H), 8.51-8.53 (m, 1 H);
MS m/e 352 (MH^+).



87

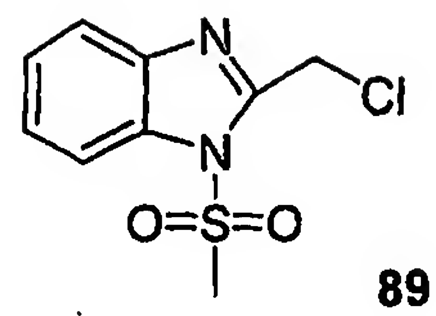
Compound **86** (130 mg, 0.37 mmol), palladium hydroxide on carbon (Pearlman's catalyst, 50 mg), EtOH (2 mL) and cyclohexene (1 mL) were stirred at reflux for 1 hour. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated and purified by flash column chromatography (gradient, CH_2Cl_2/MeOH, 30:1 to 10:1) to give 20 mg (21% yield) of compound **87** as a viscous white oil.

^1H NMR (CD_3OD) δ 2.26-2.33 (m, 2 H), 3.21-3.24 (m, 1 H), 3.65 (t, J=8.8 Hz, 1 H), 4.50-4.54 (m, 2 H), 4.67-4.70 (m, 1 H), 4.89-4.92 (m, 2 H), 7.24-7.34 (m, 2 H), 7.57 (d, J=8.0 Hz, 1 H), 7.63 (d, J=7.9 Hz, 1 H);
MS m/e 294 (MH^+).



88

Compound **88** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.

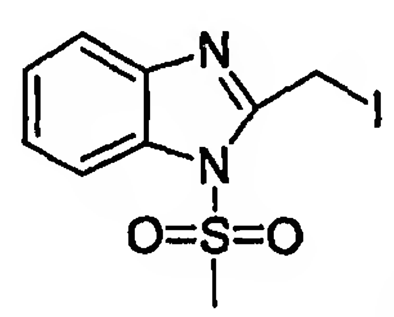


89

To a solution of 2-(chloromethyl)benzimidazole (80 g, 0.48 mol) and methanesulfonyl chloride (58.3 mL, 0.75 mol) in CH_2Cl_2 (0.5 L), triethylamine (136 mL, 0.97 mol) was added dropwise under nitrogen. The resulting mixture was stirred at room temperature for 6 hours. The mixture was filtered and the filtrate was evaporated. The residue was triturated with MeOH and filtered to afford 74.9 g (64% yield) of compound **89** as a brown solid.

^{1}H NMR ($CDCl_3$) δ 3.44 (s, 3 H), 5.11 (s, 2 H), 7.40-7.49 (m, 2 H), 7.76-7.82 (m, 1 H), 7.85-7.91 (m, 1 H);
IR (KBr, cm^{-1}) 3027, 2920, 1371, 1349, 1177, 1144, 1059;
MS m/e 245 (MH^+);

Anal. Calcd for $C_9H_9ClN_2O_2S$:		C, 44.18; H, 3.71; N, 11.45
	Found:	C, 44.09; H, 3.57; N, 11.49.



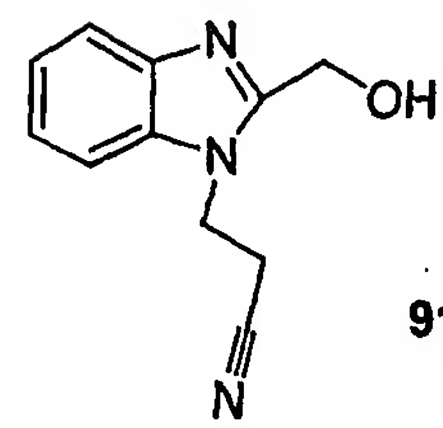
90

A solution of potassium iodide (206 g, 1.24 mol) and compound **89** (74.8 g, 0.414 mol) in acetone (1 L) was stirred at reflux under nitrogen for 4 hours. The solid was filtered and the filtrate was evaporated. The crude product was triturated in MeOH and filtered to give 83 g (60% yield) of compound **90** as a solid.

^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3 H), 4.97 (s, 2 H), 7.40-7.50 (m, 2 H), 7.75-7.85 (m, 2 H);
IR (KBr, cm^{-1}) 3022, 2916, 1366, 1173, 1055, 966, 763, 745;
MS m/e 336 (MH^+);

Anal. Calcd for $C_9H_9IN_2O_2S$: C, 32.16; H, 2.70; N, 8.33

Found: C, 32.05; H, 2.63; N, 8.22.



91

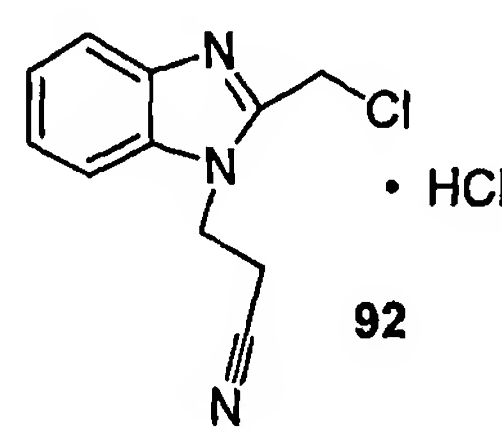
Compound **91** was prepared according to the Michael addition procedure described by Popov, I. I. in *Khim Geterotskl. Soedin.* **1996,** *6,* 781-792.

^{1}H NMR ($CDCl_3$) δ 3.08 (t, J = 6.8 Hz, 2 H), 4.63 (t, J = 6.8 Hz, 2 H), 4.77 (d, J = 5.7 Hz, 2 H), 5.73 (t, J = 5.7 Hz, 1 H), 7.17-7.28 (m, 2 H), 7.64 (d, J = 1.2 Hz, 1 H), 7.70 (d, J = 1.2 Hz, 1 H);

MS m/e 202 (MH^+);

Anal. Calcd for $C_{11}H_{11}N_3O$: C 65.66; H, 5.51; N, 20.88

Found: C, 65.94; H, 5.57; N, 21.08.



92

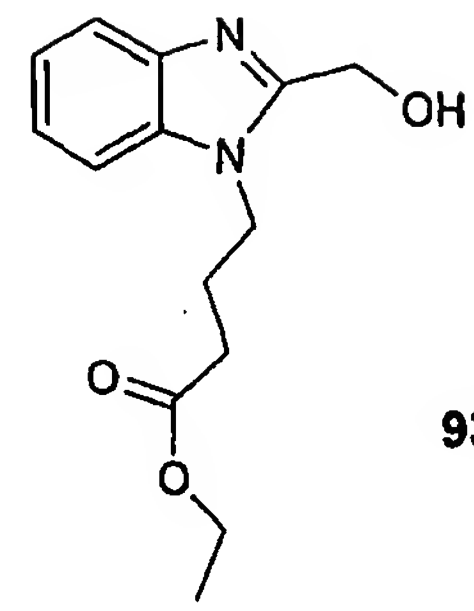
Compound **92** was prepared according to the same procedure described for compound **2.**

^{1}H NMR ($CDCl_3$) δ 3.02 (t, J = 7.0Hz, 2 H), 4.65 (t, J = 7.0 Hz, 2 H), 4.99 (s, 2 H), 7.34-7.44 (m, 3 H), 7.79-7.82 (m, 1 H);

MS m/e 220 (MH^+);

Anal. Calcd for $C_{11}H_{10}ClN_3$: C, 60.09; H, 4.65; N, 19.13

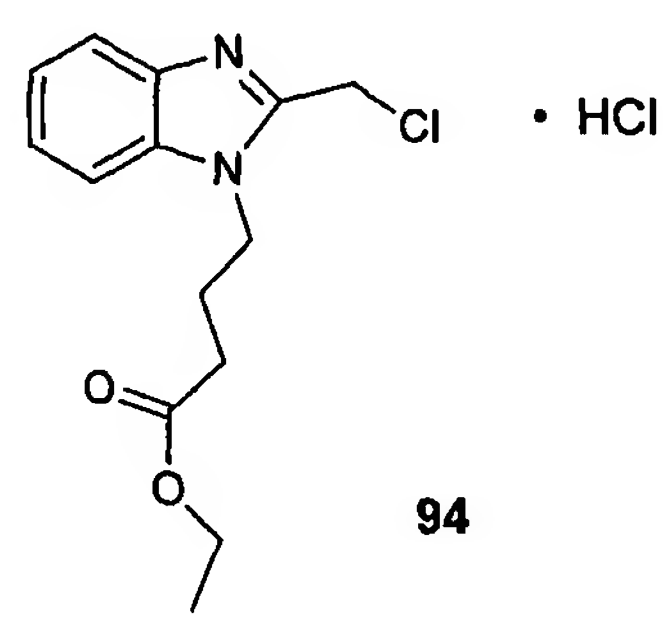
Found: C, 60.09; H, 4.65; N, 19.11.



93

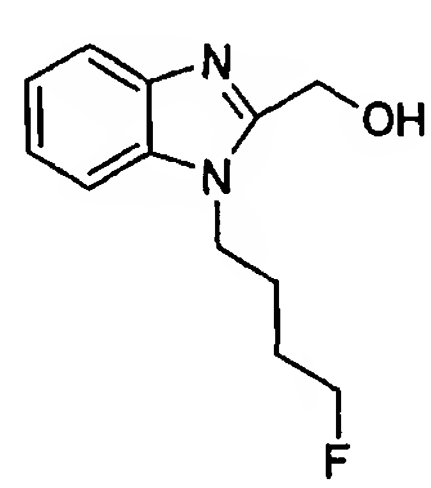
Compound **93** was prepared according to the same procedure described for compound **1** except that 4-bromobutyronitrile was replaced with ethyl 4-bromobutyrate.

^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.0 Hz, 3 H), 2.15-2.22 (m, 2 H), 2.38-2.42 (m, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 4.29-4.34 (m, 2 H), 4.96 (s, 2 H), 7.22-7.30 (m, 2 H), 7.38-7.43 (m, 1 H), 7.66-7.70 (m, 1 H);
MS m/e 250 (MH^+).



94

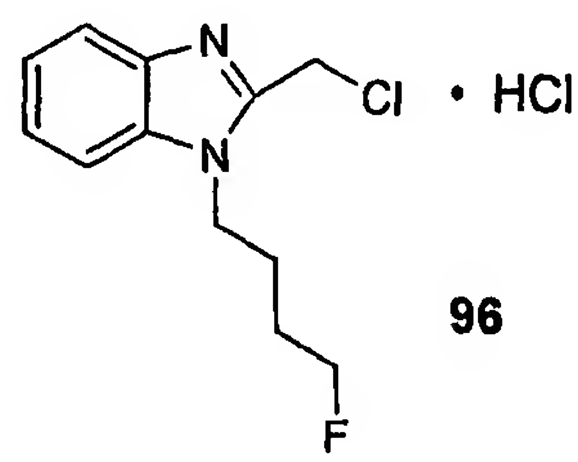
Compound **94** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.



95

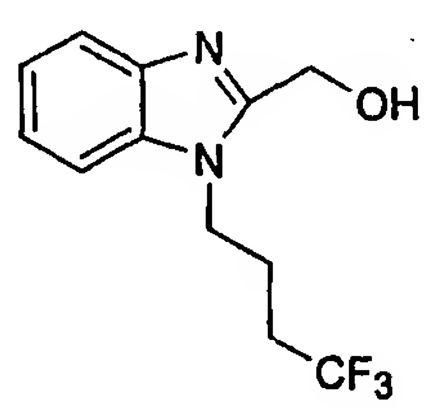
Compound **95** was prepared according to the same procedure described for compound **1** except that 4-bromobutyronitrile was replaced with 1-bromo-4-fluorobutane.

^{1}H NMR (DMSO-d_6) δ 1.65-1.75 (m, 2 H), 1.85-1.90 (m, 2 H), 4.32 (t, J = 7.5 Hz, 2 H), 4.41 (t, J = 6.0 Hz, 1 H), 4.51 (t, J = 6.0 Hz, 1H), 4.71 (d, J = 5.8 Hz, 2 H), 5.62 (t, J = 5.8 Hz, 1 H), 7.18 (t, J = 7.0 Hz, 1 H), 7.23 (t, J = 6.3 Hz, 1 H), 7.56-7.60 (m, 2 H);
MS m/e 222 (MH^+).



96

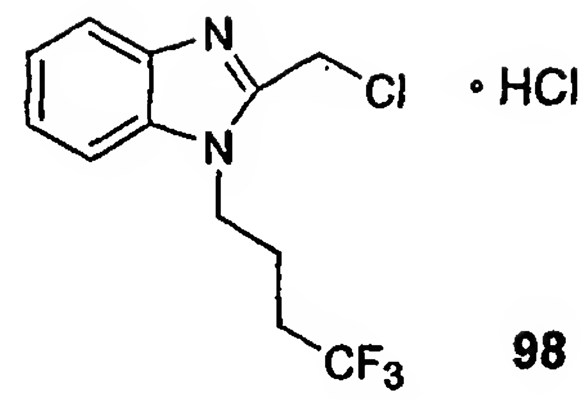
Compound **96** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.



97

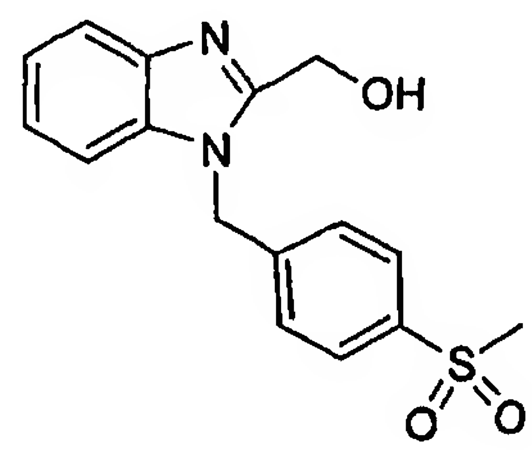
Compound **97** was prepared according to the same procedure described for compound **1** except that 4-bromobutyronitrile was replaced with 1-bromo-4,4,4-trifluorobutane.

^{1}H NMR (DMSO-d_6) δ 1.99-2.05 (m, 2 H), 2.34-2.40 (m, 2 H), 4.35-4.38 (m, 2 H), 4.73 (s, 2 H), 7.20 (t, J = 7.2 Hz, 1 H), 7.26 (t, J = 7.4 Hz, 1 H), 7.60-7.63 (m, 1 H), 7.96 (s, 1 H);
MS m/e 258 (MH^+).



98

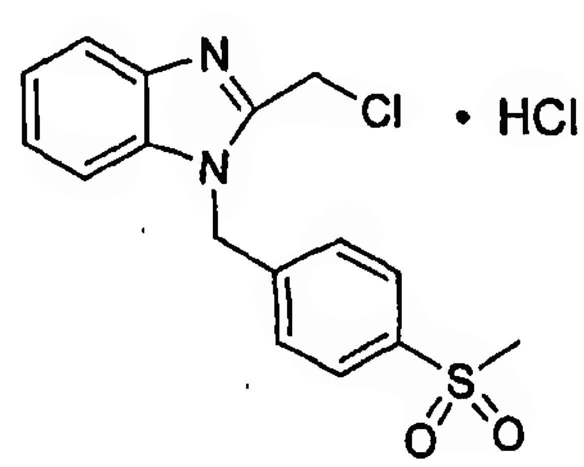
Compound **98** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.



99

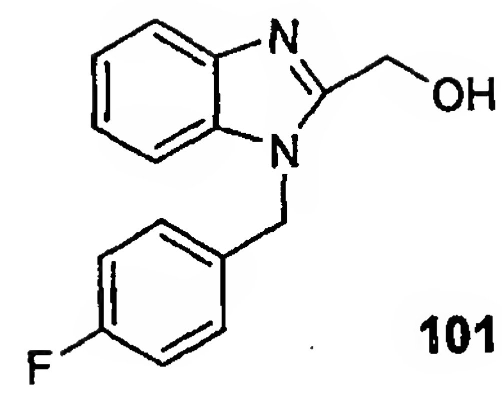
Compound **99** was prepared according to the same procedure described for compound **1** except that 4-bromobutyronitrile was replaced with 4-methylsulfonylbenzyl bromide.

^{1}H NMR (DMSO-d_6) δ 3.16 (s, 3 H), 4.75 (d, J = 5.6 Hz, 2 H), 5.70 (s, 2 H), 5.73-5.75 (m, 1 H), 7.17-7.21 (m, 2 H), 7.36-7.38 (m, 1 H), 7.42 (d, J = 8.2 Hz, 2 H), 7.64-7.65 (m, 1 H), 7.87 (d, J = 8.2 Hz, 1 H);
MS m/e 316 (MH^+).



100

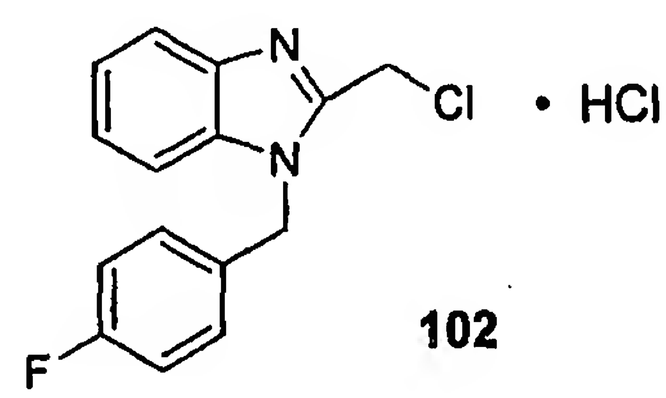
Compound **100** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.



101

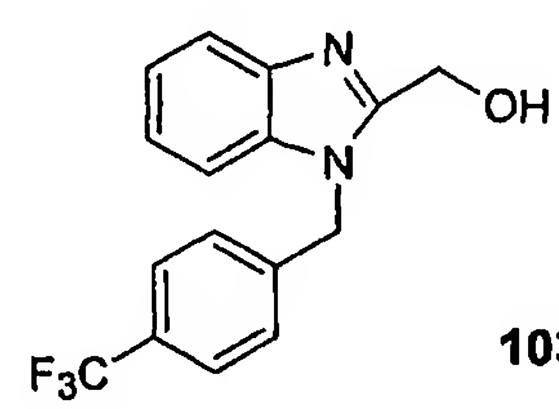
Compound **101** was prepared according to the same procedure described for compound **1** except that 4-bromobutyronitrile was replaced with 4-fluorobenzyl bromide.

^{1}H NMR (DMSO-d_6) δ 4.74 (s, 2 H), 5.55 (s, 2 H), 7.13-7.18 (m, 3 H), 7.28-7.30 (m, 2 H), 7.38-7.40 (m, 1 H), 7.59-7.63 (m, 1 H);
MS m/e 256 (MH^+).



102

Compound **102** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.

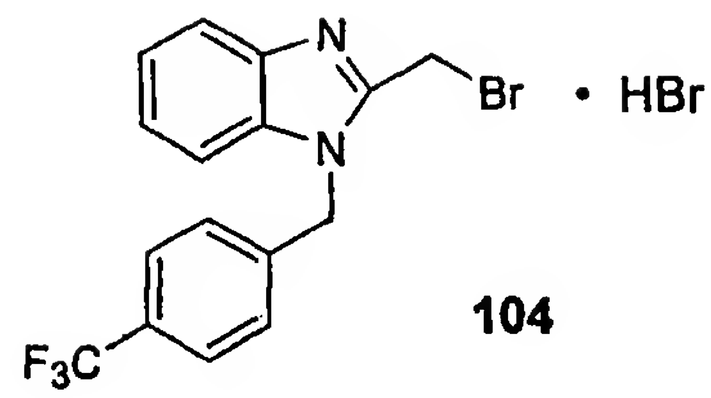


103

Compound **103** was prepared according to the same procedure as compound **1** except that 4-bromobutyronitrile was replaced with 4-trifluoromethylbenzyl bromide.

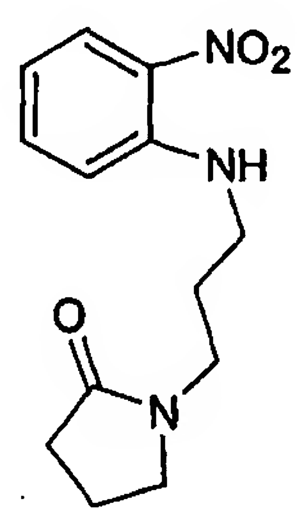
^{1}H NMR (DMSO-d_6) δ 4.74 (s, 2 H), 5.68 (s, 2 H), 7.11-7.20 (m, 2 H), 7.35-7.39 (m, 2 H), 7.62-7.64 (m, 1 H), 7.64-7.72 (m, 2 H);

MS m/e 369 (MH^+).



104

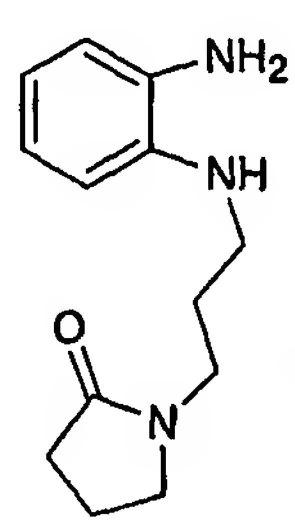
Compound **104** was prepared according to the same procedure described for compound **64** and was used immediately upon isolation.



105

Compound **105** was prepared according to the same procedure described for compound **16** using 1-(3-aminopropyl)-2-pyrrolidinone instead of 3-(methylthio)propylamine.

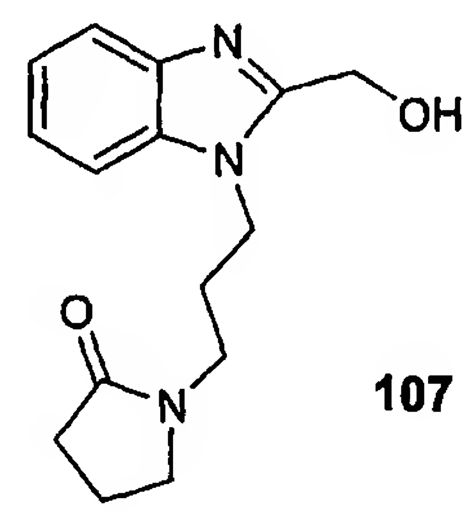
^{1}H NMR ($CDCl_3$) δ 1.93 (m, 2 H), 2.02-2.07 (m, 2 H), 2.39 (t, J = 8.05 Hz, 2 H), 3.32-3.36 (m, 2H), 3.36-3.45 (m, 4 H), 6.64 (t, J = 7.0 Hz, 1 H), 6.83 (d, J = 8.7 Hz, 1 H), 7.42 (t, J = 8.7 Hz, 1 H), 8.07 (bs, 1 H), 8.16 (d, J = 7.0 Hz, 1 H);
MS m/e 263 (MH^+);
Anal. Calcd for $C_{13}H_{17}N_3O_3$•0.24 H2O: C, 58.34; H, 6.58; N, 15.70
Found: C, 58.05; H, 6.20; N, 11.41.



106

Compound **106** was prepared according to the same reduction procedure described for compound **13**.

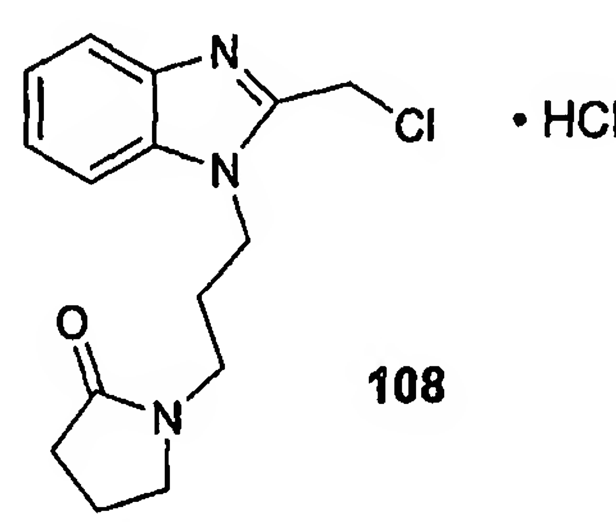
^{1}H NMR ($CDCl_3$) δ 1.83-1.88 (m, 2 H), 1.99-2.05 (m, 2 H), 2.41 (t, J = 8.0 Hz, 2 H), 3.16 (t, J = 6.5 Hz, 2 H), 3.33-3.43 (m, 4 H), 6.63-6.65 (m, 2 H), 6.70 (d, J = 7.1 Hz, 1 H), 6.78 (t, J = 7.5 Hz, 1 H), 7.26 (s, 1 H);
MS m/e 233 (MH^+).



107

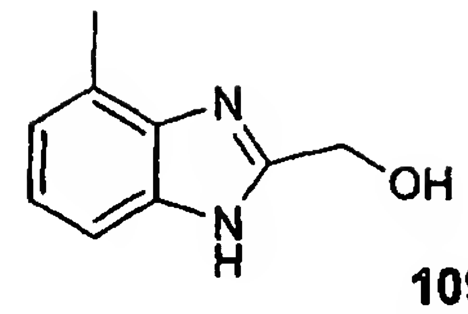
Compound **107** was prepared according to the same procedure described for compound **14**.

^{1}H NMR (DMSO-d_6) δ 1.87-1.92 (m, 2 H), 1.95-2.00 (m, 2 H), 2.21 (t, J = 8.0 Hz, 2 H), 3.25-3.34 (m, 4 H), 4.26 (t, J = 7.6 Hz, 2 H), 4.72 (s, 2 H), 5.65 (bs, 2 H);
MS m/e 273 (MH^+).



108

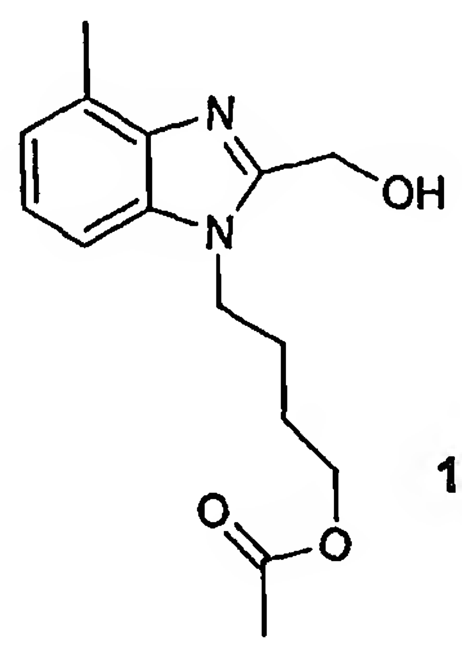
Compound **108** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.



109

A mixture of 2,3-diaminotoluene (10.21 g, 83.57 mmol) and glycolic acid (9.53 g, 125.36 mmol) in 6 N HCl (100 mL) were stirred at 100 °C for 14 hours. The reaction mixture was cooled and made basic (pH 7-8) with ammonium hydroxide. A dark brown solid was collected by filtration, washed with H_2O, and dried to give 12.47 g (92% yield) of compound **109**.

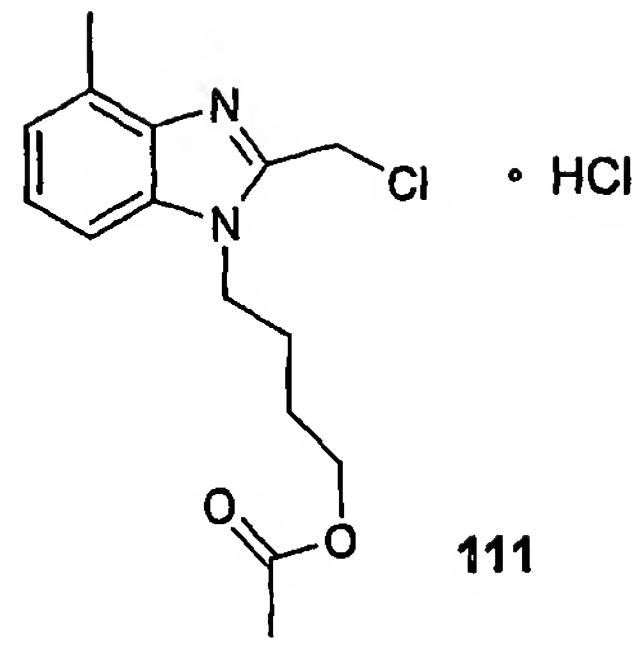
^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3 H), 4.70 (s, 2 H), 6.93 (d, J = 7.3 Hz, 1 H), 7.04 (t, J = 7.6 Hz, 1 H), 7.31 (d, J = 7.9 Hz, 1 H).



110

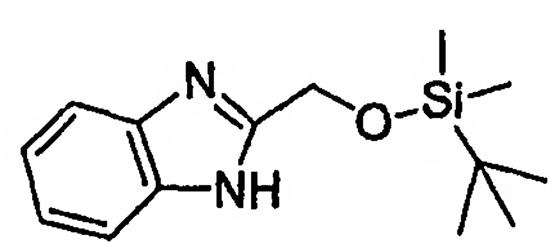
Compound **110** was prepared according to the same procedure described for compound **24** except that the base employed was cesium carbonate.

^{1}H NMR ($CDCl_3$) δ 1.67-1.73 (m, 2 H), 1.89-1.96 (m, 2 H), 2.02 (s, 3 H), 2.59 (s, 3 H), 4.05-4.10 (m, 2 H), 4.27 (t, J = 7.5 Hz, 2 H), 4.89 (s, 2 H), 7.01-7.03 (m, 1 H), 7.12-7.15 (m, 2 H);
MS m/e 277 (MH^+).



111

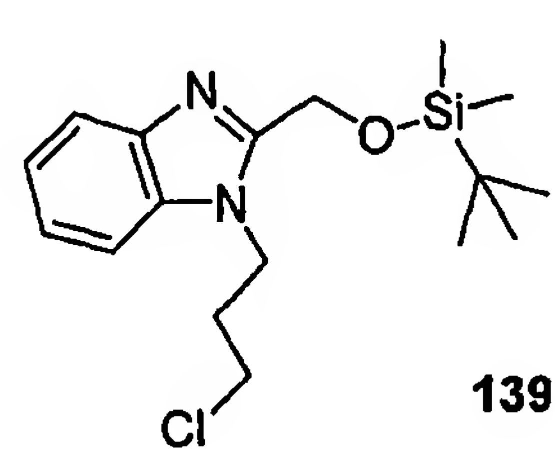
Compound **111** was prepared according to the same procedure described for chloride **2** and was used immediately upon isolation.
MS m/e 295 (MH^+).



138

To a solution of 2-hydroxymethylbenzimidazole (5.92 g, 40.0 mmol) and imidazole (6.81 g, 100.0 mmol) in THF (100 mL) was added *t*-butyldimethylsilyl chloride (12.65 g, 84.0 mmol) in several portions. The resulting mixture was stirred at room temperature for 2 hours and filtered. The filtrate was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was recrystallized from hexanes/EtOAc to give 8.50 g (81%) of compound **138** as white needles.

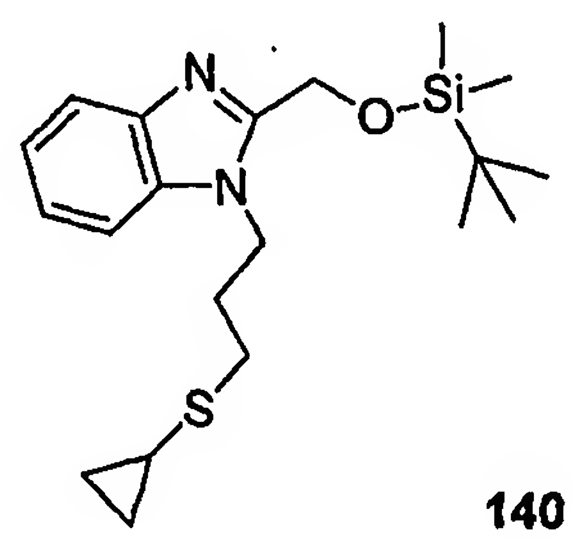
^{1}H NMR ($CDCl_3$) δ 0.15-0.16 (m, 6 H), 0.95-0.97 (m, 9 H), 5.02-5.03 (m, 2 H), 7.24-7.27 (m, 2 H), 7.59 (bs, 2 H);
MS m/e 263 (MH^+).



139

Compound **139** was prepared according to the same procedure described for compound **68** except that cesium carbonate was used instead of sodium hydride as the base.

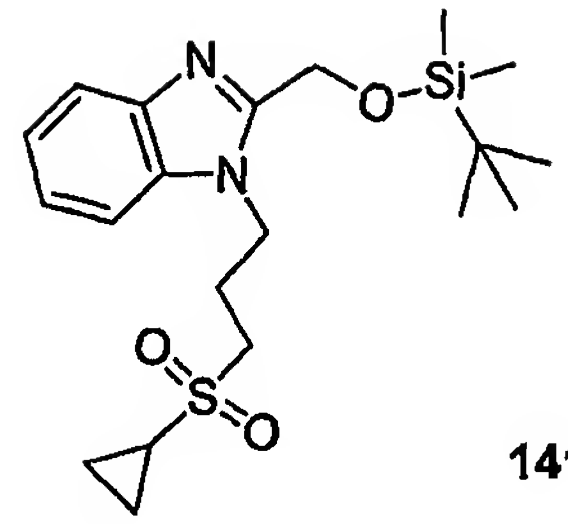
^{1}H NMR ($CDCl_3$) δ 0.13-0.14 (m, 6 H), 0.91-0.92 (m, 9 H), 2.35-2.37 (m, 2 H), 3.58 (t, J = 6.0 Hz, 2 H), 4.50 (t, J = 7.0 Hz, 2 H), 5.01 (s, 2 H), 7.26-7.32 (m, 2 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.77 (d, J = 10.0 Hz, 1 H);
MS m/e 339 (MH^+).



140

Compound **140** was prepared through the coupling of compound **139** and cyclopropylsulfide according to the same procedure described for compound **74** except using cesium carbonate instead of sodium hydride as the base. The cyclopropylsulfide was prepared according to a literature procedure by E. Block, A. Schwan, and D. Dixon in *Journal of the American Chemical Society*, **1992**, *114*, 3492-3499.

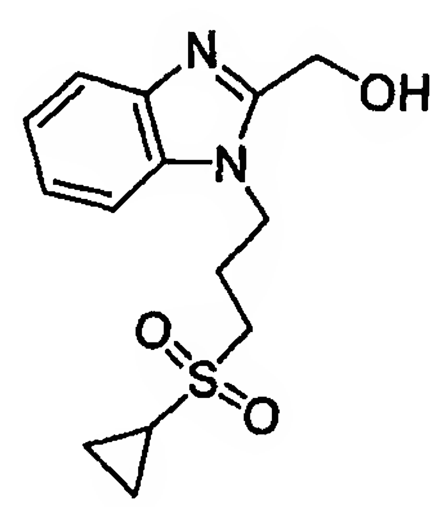
^{1}H NMR ($CDCl_3$) δ 0.12-0.13 (m, 6 H), 0.54-0.56 (m, 2 H), 0.84-0.86 (m, 2 H), 0.90-0.91 (m, 9 H), 1.87-1.92 (m, 1 H), 2.20-2.25 (m, 2 H), 2.62 (t, J = 7.0 Hz, 2 H), 4.43 (t, J = 7.4 Hz, 2 H), 5.00 (s, 2 H), 7.26-7.32 (m, 2 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.77 (d, J = 10.0 Hz, 1 H);
MS m/e 377 (MH^+).



141

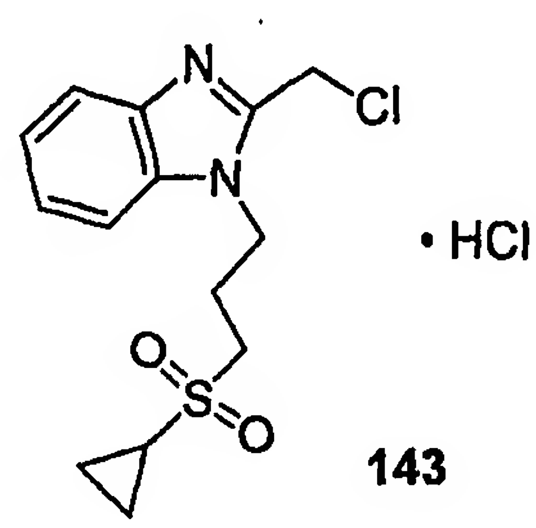
Compound **141** was prepared from compound **140** by the same procedure described for compound **18.**

^{1}H NMR ($CDCl_3$) δ 0.13-0.14 (m, 6 H), 0.91-0.92 (m, 9 H), 1.01-1.03 (m, 2 H), 1.23-1.24 (m, 2 H), 2.31-2.34 (m, 1 H), 2.48-2.52 (m, 2 H), 3.07 (t, J = 7.2 Hz, 2 H), 4.51 (t, J = 7.1 Hz, 2 H), 5.00 (s, 2 H), 7.26-7.32 (m, 2 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.77 (d, J = 10.0 Hz, 1 H);
MS m/e 409 (MH^+).



142

To solution of compound **141** (27 mg, 0.07 mmol) in THF (0.5 ml) was added TBAF (1 M THF solution, 0.13 mL, 0.13 mmol) at 0 °C and the mixture was stirred for 10 minutes. The solvent was evaporated and the residue was passed through a short plug of silica (CH_2Cl_2/MeOH, 10:1) to give crude compound **142** which was used immediately upon isolation.

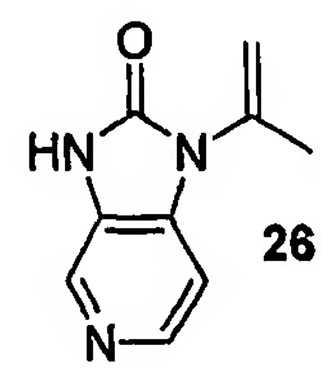


143

Compound **143** was prepared according to the same procedure described for compound **2** and was used immediately upon isolation.

II. Preparation of 2-Oxo-imidazopyridines and 2-Oxo-imidazopyrimidines:

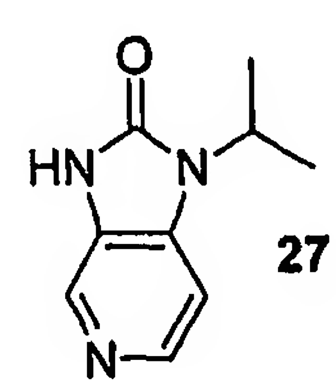
Compounds **26-58** and **112-126** are intermediates prepared according to the procedures depicted in Scheme III.



26

3,4-Diaminopyridine (30 g, 274.9 mmol), ethyl acetoacetate (53.66 g, 412 mmol) and DBU (1 mL) were stirred at reflux in xylene (300 mL) under a Dean-Stark trap. After stirring for 3.5 hours, the solvent was evaporated and the residue was purified by flash chromatography (EtOAc; EtOAc:MeOH = 10:1) to give a solid which was recrystallized from CH_2Cl_2/EtOAc to afford **26** (21.45 g, 45% yield) as white crystals.

^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3 H), 5.22 (s, 1 H), 5.46 (s, 1 H), 7.19 (d, J = 5.4 Hz, 1 H), 8.20 (d, J = 5.4 Hz, 1 H), 8.23 (s, 1 H);
MS m/e 176 (MH^+).

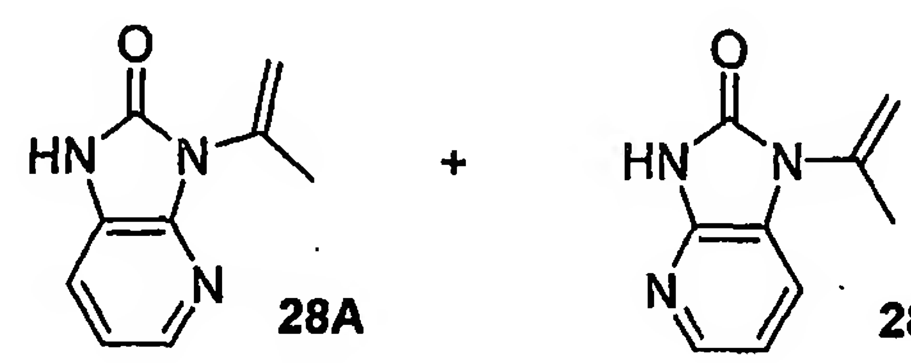


27

Compound **26** (1.0 g, 5.71 mmol) in the presence of 10 % palladium on carbon (0.1 g) in MeOH (10 mL) was hydrogenated in a Parr shaker at 40 psi for

2 days. The catalyst was removed by filtration and the filtrate was evaporated to give compound **27** as a white solid.

^{1}H NMR ($CDCl_3$) δ 1.57 (d, J = 7.0 Hz, 6 H), 4.72-4.76 (m, 1 H), 7.19 (d, J = 5.8 Hz, 1 H), 8.30 (d, J = 5.8 Hz, 1 H), 8.58 (s, 1 H);
MS m/e 178 (MH^+).



28A + 28B

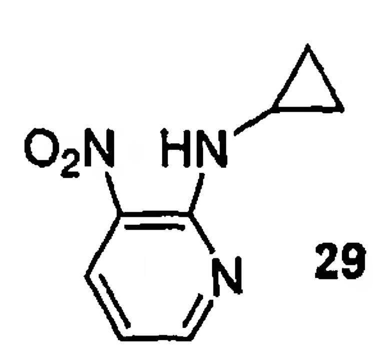
The same procedure described for compound **26** was carried out using 2,3-diaminopyridine to give **28A** and **28 B** which were separated by flash chromatography (gradient, CH_2Cl_2/acetone,5:1 to 4:1).

Compound **28A**

^{1}H NMR (CD_3OD) δ 2.31 (s, 3 H), 5.40 (s, 1 H), 5.51 (s, 1 H), 7.04 (dd, J = 5.2, 7.7 Hz, 1 H), 7.38 (dd, J = 1.4, 7.7 Hz, 1 H), 8.09 (dd, J = 1.4, 5.2 Hz, 1 H);
MS m/e 176 (MH^+).

Compound **28B**

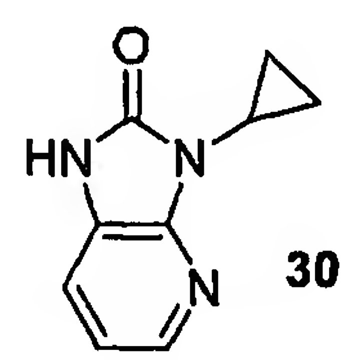
^{1}H NMR (CD_3OD) δ 2.26 (s, 3 H), 5.21 (s, 1 H), 5.38 (s, 1 H), 7.11 (dd, J = 5.5, 7.9 Hz, 1 H), 7.40 (dd, J = 1.3, 7.9 Hz, 1 H), 8.09 (dd, J = 1.3, 5.5 Hz, 1 H);
MS m/e 176 (MH^+).



29

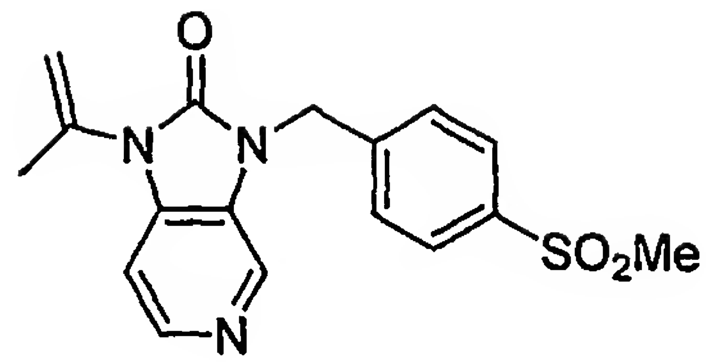
2-Chloro-3-nitropyridine (7.0 g, 50.0 mmol), cyclopropylamine (3.71g, 65 mmol) and potassium carbonate (13.82 g, 100 mmol) were stirred in CH_3CN (100 mL) at room temperature overnight and at reflux for an additional hour. The solid was filtered and the filtrate was evaporated. Water was added to the residue and the mixture was extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and filtered. Evaporation of the solvent gave **29** (8.40 g, 94% yield) as a dark brown solid.

^{1}H NMR (CD_3OD) δ 0.63-0.69 (m, 2 H), 0.93-0.97 (m, 2 H), 3.01-3.06 (m, 1 H), 6.70-6.72 (dd, J = 4.5, 8.3 Hz, 1 H), 8.24 (bs, 1 H), 8.42 (dd, J = 1.7, 8.3 Hz, 1 H), 8.52 (dd, J = 1.7, 4.5 Hz, 1 H);
MS m/e 180 (MH^+).


30

Compound **29** (8.29 g, 46.28 mmol) was reduced with iron using the procedure described for compound **7**. To the crude diamine in THF (50 mL) was added 1 equivalent of carbonyldiimidazole and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc / hexane,1:1 to EtOAc / MeOH, 10: 1) to give **30** (1.93 g, 24 % yield over two steps) as a light orange solid.

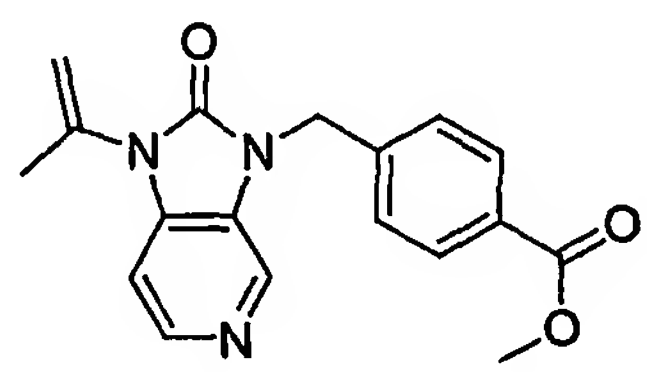
^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 3.4 Hz, 2 H), 1.20 (s, 2H), 3.01-3.04 (m, 2 H), 7.02 (dd, J = 5.3, 7.7 Hz, 1 H), 7.32 (dd, J = 1.4, 7.7 Hz, 1 H), 8.12 (dd, J = 1.4 Hz, 5.3 Hz, 1 H), 9.61 (bs, 1 H);
MS m/e 176 (MH^+).



31

A mixture of **26** (2.0 g, 11.4 mmol), Cs_2CO_3 (5.58 g, 17.1 mmol) and *p*-methylsulfonylbenzyl chloride (2.34 g, 11.4 mmol) in acetone (50 mL) was stirred at reflux for 2 hours. The solid was removed by filtration and the filtrate was evaporated. The residue was purified by flash chromatography (gradient, CH_2Cl_2/MeOH, 40:1 to 20:1) to afford **31** (3.24 g, 83% yield) as a white solid.

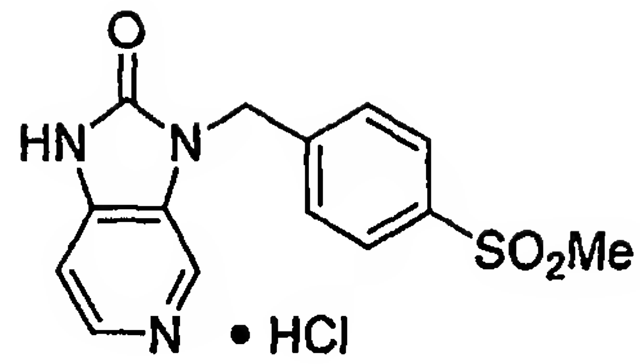
^{1}HNMR (DMSO-d_6) δ 2.18 (s, 3 H), 3.20 (s, 3 H), 5.23 (s, 2 H), 5.26 (s, 1 H), 5.45 (d, J = 1.2 Hz, 1 H)), 7.21 (d, J = 5.3 Hz, 1 H), 7.63 (d, J = 8.4 Hz, 2 H), 7.92 (d, J = 8.4 Hz, 2 H), 8.25 (d, J = 5.1 Hz, 1H), 8.41 (s, 1 H);
MS m/e 344 (MH^+).



32

Compound **32** was prepared using the same procedure for compound **31**, except that methylsulfonylbenzyl chloride was replaced with methyl *p*-bromomethylbenzoate.

^{1}HNMR (DMSO-d_6) δ 2.05 (s, 3H), 3.70 (s, 3H), 5.06 (s, 2H), 5.12 (s, 1H), 5.32 (d, J=1.4 Hz, 1H), 7.07-7.09 (dd, J= 0.45, 5.4 Hz, 1H), 7.37 (d, J=8.4 Hz, 2H), 7.80-7.82 (m, 2H), 8.11 (d, J=5.3 Hz, 1H), 8.23 (s, 1H);
MS m/e 324 (MH^+).

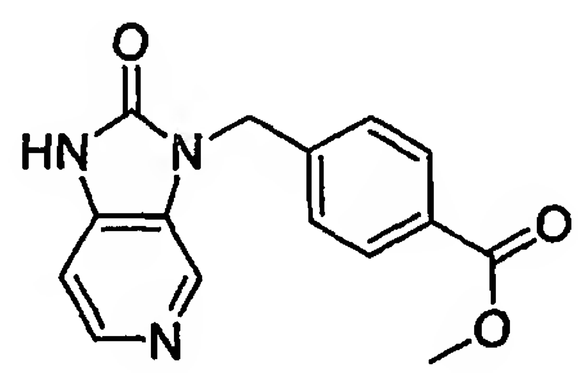


33

A solution of **31** (3.24 g, 9.45 mmol) in concentrated HCl (5 ml) and MeOH (50 ml) was stirred at reflux for 2 hours. The solvent was evaporated and the residue was triturated in hot MeOH to yield **33** (2.80 g, 87% yield) as a white solid as the HCl salt.

^{1}HNMR (DMSO-d_6) δ 3.18 (s, 3 H), 5.17 (s, 2 H), 7.07 (d, J = 5.2 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 2 H), 7.91 (d, J = 8.2 Hz, 2 H), 8.17 (d, J = 5.0 Hz, 1 H), 8.29 (s, 1 H);

MS m/e 304 (MH^+).

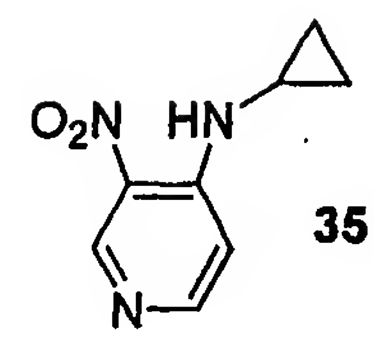


34

A solution of **32** (1.30 g, 4.02 mmol) in concentrated HCl (10 ml) and MeOH (10 ml) was stirred at reflux for 1 hour. The solution was neutralized with K_2CO_3 to pH 6, and extracted with EtOAc. The organic layer was dried and evaporated to dryness. The crude product was triturated with hot CH_2Cl_2 to yield **34** (0.85 g, 75% yield) as off-white solid.

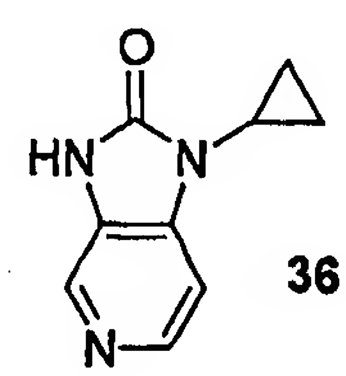
^{1}H NMR (DMSO-d_6) δ 3.90 (s, 3 H), 5.20 (s, 2 H), 7.13 (d, J = 5.2 Hz, 1 H), 7.53 (d, J = 8.2 Hz, 2 H), 8.00 (d, J = 8.2 Hz, 2 H), 8.22 (d, J = 5.2 Hz, 1 H), 8.31 (s, 1 H);

MS m/e 284 (MH^+).


35

A solution of 4-methoxy-3-nitro-pyridine (7.71 g, 50 mmol) and cyclopropylamine (7.14g, 125 mmol) in EtOH (20 mL) was stirred at reflux under a dry-ice trap condenser for 2 hours. The solvent was evaporated to give **35** as a yellow solid.

^{1}H NMR (CD_3OD) δ 0.72-0.75 (m, 2 H), 0.99-1.03 (m, 2 H), 2.63-2.68 (m, 1 H), 7.19 (d, J = 6.2 Hz, 1 H), 8.26 (bs, 1 H), 8.35 (d, J = 6.2 Hz, 1 H), 9.22 (s, 1 H); IR (KBr, cm^{-1}) 3369, 1613, 1560, 1515, 1406, 1254, 1195, 1039, 881, 846, 769, 545; MS m/e 180 (MH^+).


36

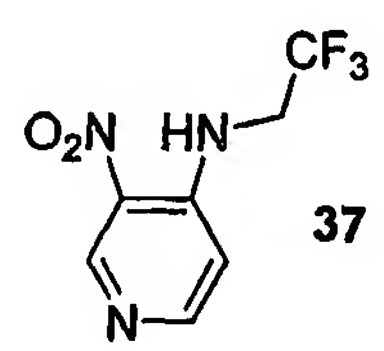
To a solution of **35** (12.28 g, 68.6 mmol) in anhydrous MeOH (120 mL) was added 10% palladium on carbon (3 g) in several portions under nitrogen. The reduction was carried out using a balloon containing hydrogen (1 atm) for 16 hours. The catalyst was removed by filtration through a pad of Celite and rinsed with MeOH. The filtrate was concentrated to a slurry and Et_2O was added to precipitate the diamine product as a light yellow solid (10.1g, 99% yield).

To a slurry of the diamine and polyvinylpyridine (22.0 g) in acetonitrile (70 mL) of a 20% phosgene solution in toluene was added dropwise (70 mL, 135.4 mmol). After stirring at room temperature for 2 hours, the reaction was quenched with water. Polyvinylpyridine was removed by filtration and rinsed

with MeOH. The filtrate was concentrated and Et_2O was added to precipitate product **36** (15.5g, 98% yield) as a light brown solid.

^{1}H NMR (CD_3OD) δ 0.95-0.98 (m, 2 H), 1.07-1.14 (m, 2 H), 2.91-2.96 (m, 1 H), 7.32 (dd, J = 0.5, 5.3 Hz, 1 H), 7.18 (s, 1 H), 8.21 (d, J = 5.3 Hz, 1 H);
MS m/e 176 (MH^+).

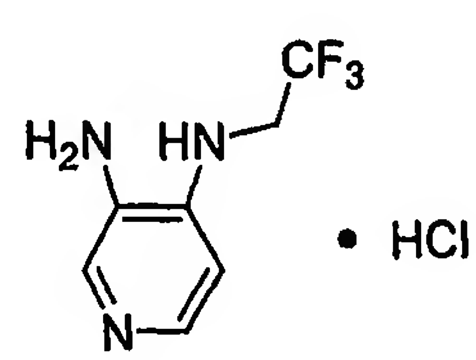
2-Oxo-imidazopyridine **39** was prepared using the same procedure described for the preparation of **36**, except that cyclopropylamine was replaced with 2 equivalents of trifluoroethylamine hydrochloride and diisopropylethylamine, and the reaction was carried out in a sealed tube at 120-130 °C for 2 days.



37

^{1}H NMR ($CDCl_3$) δ 4.02 (q, J = 7.9 Hz, 2 H), 6.83 (d, J = 5.5 Hz, 1 H), 8.43 (d over bs, 2 H), 9.28 (s, 1 H);
IR (KBr, cm^{-1}): 3287, 3241, 1629, 1611, 1363, 1254, 1150, 1047, 870;
MS m/e 222 (MH^+);

Anal. Calcd for $C_7H_6F_3N_3O_2$:		C, 38.02; H, 2.73; N, 19.00
	Found:	C, 38.00; H, 2.69; N, 19.19.



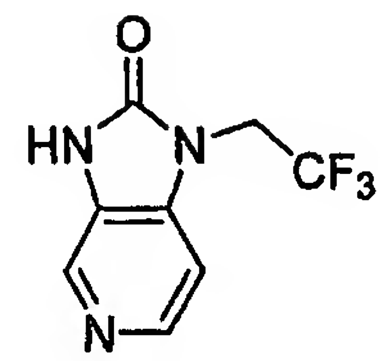
38

^{1}H NMR (CD_3OD) δ 4.23 (q, J = 9.0 Hz, 2 H), 7.05 (d, J = 6.6 Hz, 1 H), 7.74 (d, J = 1.1 Hz, 1 H), 7.84 (d, J = 1.1, 6.6 Hz, 1 H);
IR (KBr, cm^{-1}): 3343, 3202, 3062, 1625, 1578, 1529, 1257, 1154, 949;

MS m/e 192 (MH^+);

Anal. Calcd for $C_7H_8F_3N_3 \bullet HCl$: C, 36.94; H, 3.99; N, 18.46

Found: C, 37.19; H, 3.86; N, 18.79.



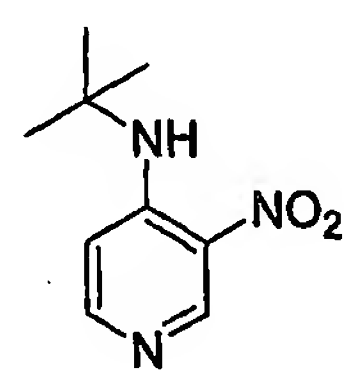
39

^1H NMR (DMSO-d_6) δ 4.99 (q, J = 9.2 Hz, 2 H), 7.90 (d, J = 6.3 Hz, 1 H), 8.61 (d, J = 6.3 Hz, 1 H), 8.63 (s, 1 H);

IR (KBr, cm^{-1}): 3423, 2994, 1744, 1517, 1347, 1254, 1263, 1173, 1000, 811;

MS m/e 218 (MH^+).

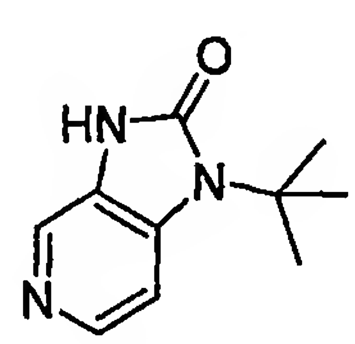
2-Oxo-imidazopyridine **41** was prepared using the same procedure described for compound **36**, except that cyclopropylamine was replaced with t-butylamine and the reaction was carried out in a sealed tube at 80 °C. This compound was used as a crude intermediate for the coupling reaction.



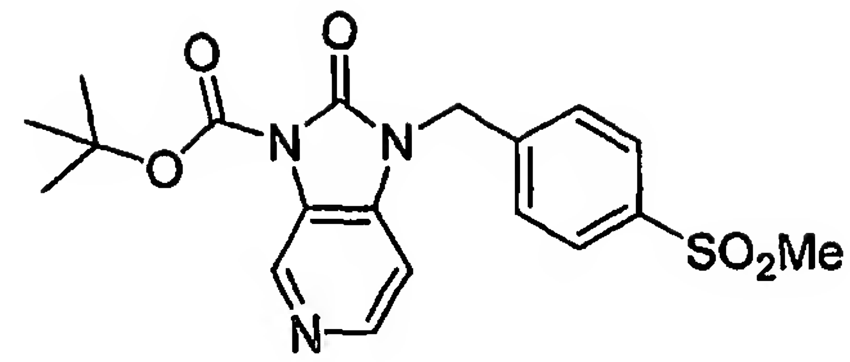
40

^1H NMR ($CDCl_3$) δ 1.54 (s, 9 H), 7.21 (d, J = 6.3 Hz, 1 H), 8.17 (d, J = 6.3 Hz, 1 H), 9.08 (s, 1 H);

MS m/e 196 (MH^+).



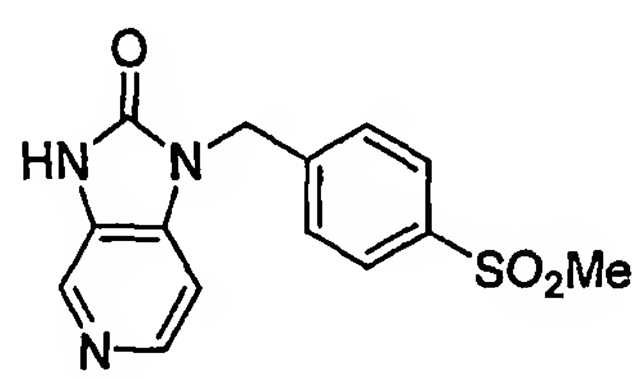
41



42

A mixture of 1,2-dihydro-2-oxo-3*H*-imidazol[4,5-c]pyridine-3-carboxylic acid, 1,1-dimethyl ethyl ester (470 mg, 2.0 mmol) (prepared according to the procedure described by N. Meanwell et al. in *J. Org. Chem.* **1995**, *60*, 1565), Cs_2CO_3 (978 mg, 3.0 mmol) and *p*-methylsulfonylbenzyl chloride (451 mg, 2.2 mmol) in acetone (10 mL) was stirred at reflux for 2 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography (gradient, CH_2Cl_2/MeOH, 40:1 to 20 :1) to afford **42** (500 mg, 62% yield) as a white solid.

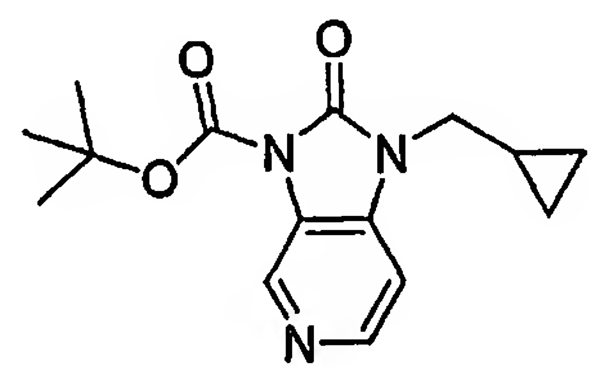
^{1}H NMR ($CDCl_3$) δ 1.71 (s, 9 H), 3.04 (s, 3 H), 5.15 (s, 2 H), 6.90 (m, 1 H), 7.54 (m, 2 H), 7.93 (m, 2 H), 8.40 (m, 1 H), 9.01 (m, 1 H);
MS m/e 404 (MH^+).



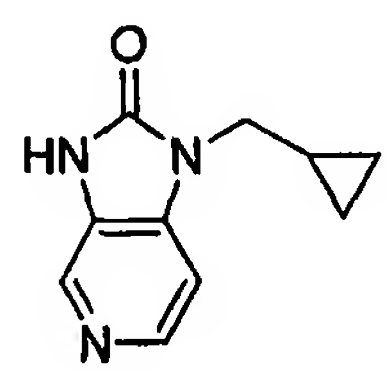
43

A mixture of **42** (260 mg, 0.64 mmol) and 1 N NaOH (3.22 ml) in THF (5 ml) and water (1 ml) was stirred at the ambient temperature overnight. The mixture was diluted with saturated NH_4Cl and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was triturated with EtOAc to produce **43** (180 mg, 93% yield) as a white solid.
^{1}H NMR (DMSO-d_6) δ 3.34 (s, 3 H), 5.16 (s, 2 H), 7.19 (d, J = 5.2 Hz, 1 H), 7.56 (d, J = 8.4 Hz, 2 H), 7.89 (d, J = 8.4 Hz, 2 H), 8.15 (d, J = 5.2 Hz, 1 H), 8.22 (s, 1 H), 11.34 (s, 1 H);
MS m/e 304 (MH^+).

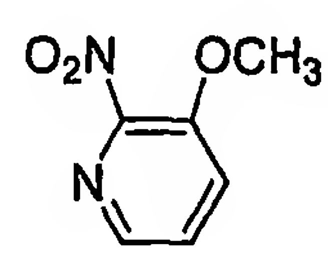
2-Oxo-imidazopyridine **45** was prepared using the same procedure for compound **43**, except that *p*-methylsulfonylbenzyl chloride was replaced with cyclopropylmethyl bromide. This compound was used as a crude intermediate for the coupling reaction.


44

^{1}H NMR (CD_3OD) δ 0.44-0.45 (m, 2 H), 0.56-0.58 (m, 2 H), 1.21-1.25 (m, 1 H), 1.69 (s, 9 H), 3.79 (d, J = 7.1 Hz, 2 H), 7.35 (d, J = 5.4 Hz, 1 H), 8.34 (d, J = 5.4 Hz, 1 H), 8.84 (s, 1 H);
MS m/e 290 (MH^+).


45

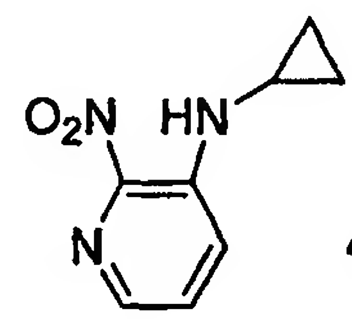
^{1}H NMR (CD_3OD) δ 7.54 (d, J = 1.2 Hz, 1 H), 8.19 (d, J = 1.2 Hz, 1 H), 8.23 (s, 1 H), 8.67 (s, 1 H);
MS m/e 137 (MH^+).


46

To a solution of 3-hydroxy-2-nitropyridine (100 g, 0.71 mol) in acetone (800 mL) was added potassium carbonate (148 g, 1.07 mol) followed by dimethyl sulfate (99 g, 0.79 mol). The reaction mixture was stirred vigorously using a mechanical stirrer and heated to 60 °C for 4.5 hours. The mixture was filtered while still warm. The filtrate was stripped of solvent to give a crude

brown solid. The solid was diluted with water and extracted with EtOAc. The organic extracts were dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 1:1) to give **46** as a bright yellow solid (81 g, 74 % yield).

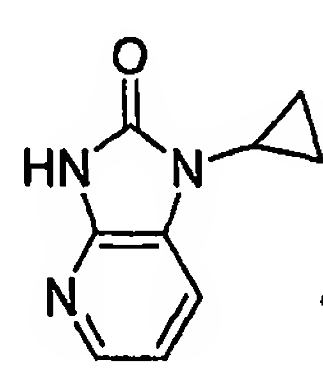
^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3 H), 7.51-7.57 (m, 2 H), 8.10 (dd, J = 1.5, 7.5 Hz, 1 H);
MS m/e 155 (MH^+).



47

Compound **47** was obtained from **46** using the same procedure for the preparation of **35** except that the reaction was carried out with 1.5 equivalents of cyclopropylamine in a sealed tube at 120 °C for 2 days.

^{1}H NMR ($CDCl_3$) δ 0.67-0.72 (m, 2 H), 0.89-1.00 (m, 2 H), 2.58-2.65 (m, 1 H), 7.50 (dd, J = 4.0, 8.6 Hz, 1 H), 7.82 (J = 8.6 Hz, 1 H), 7.83 (d, J = 8.6 Hz, 1 H), 7.97 (dd, J = 1.4, 4.0 Hz, 1 H);
MS m/e 155 (MH^+).

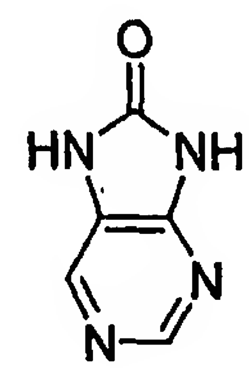


48

A solution of **47** (300 mg, 1.67 mmol) in MeOH (25 mL) was agitated under H_2 (10 psi) in the presence of 10% palladium on carbon (60 mg) for 15 min. The catalyst was removed by filtration through a pad of Celite. To the filtrate was added urea (402 mg, 6.70 mmol), and the mixture was evaporated. The solid residue was then heated at 170 °C for 16 hours. The resulting black

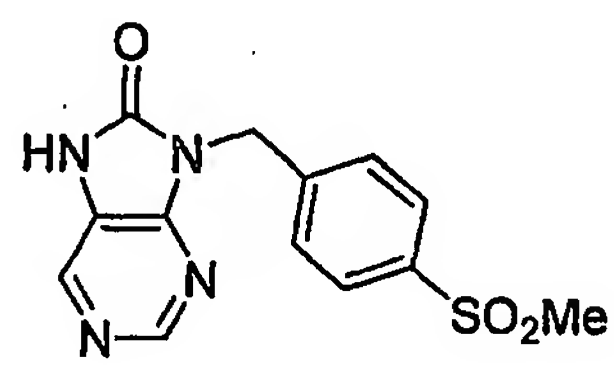
solid was heated in boiling ethanol and filtered. The filtrate was evaporated and the residue was purified by flash chromatography (gradient, straight CH_2Cl_2 to CH_2Cl_2/MeOH, 20:1) to give compound **48** as a yellow solid (82 mg, 28% yield).

^{1}H NMR ($CDCl_3$) δ 0.99-1.04 (m, 2 H), 1.12-1.15 (m, 2 H), 2.89-2.93 (m, 1 H), 7.05 (dd, J = 5.3, 7.8 Hz, 1 H), 7.41 (dd, J = 1.3; 7.8 Hz, 1 H), 8.05 (d, J = 5.3 Hz, 1 H);
MS m/e 176 (MH^+).



49

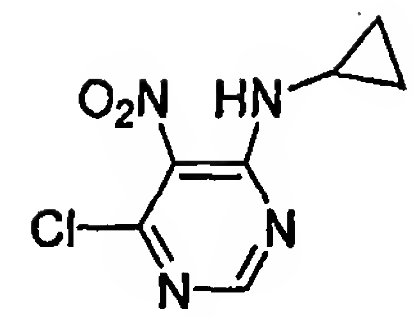
Compound **49** was prepared from 4,5-diaminopyrimidine and urea using the same procedure described for compound **48.**



50

To a slurry of **49** (136 mg, 1.0 mmol) in THF (5 mL) was added BTPP (946 mg, 3.0 mmol) and *p*-methylsulfonylbenzyl chloride (205 mg, 1.0 mmol) at ambient temperature. After stirring overnight, the solution was diluted with EtOAc, washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, CH_2Cl_2/MeOH, 40:1 to 20:1) to afford compond **50** (52 mg, 34% yield) as a white solid.

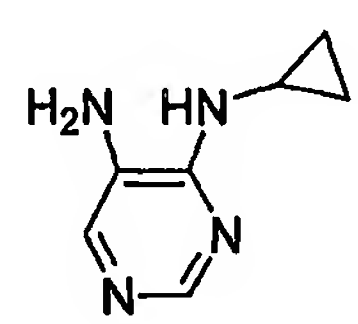
^{1}H NMR (CD_3OD) δ 3.08 (s, 3 H), 5.26 (s, 2 H), 7.67 (d, J = 8.4 Hz, 2 H), 7.91-7.93 (m, 2 H), 8.34 (s, 1 H), 8.74 (s, 1 H);
MS m/e 305 (MH^+).



51

To a suspension of 4,6-dichloro-5-nitropyrimidine (3.88 g, 20.0 mmol) and triethylamine (4.05 g, 40.0 mmol) in THF (50 ml) was added cyclopropylamine (1.14 g, 20.0 mmol) dropwise at 0 ^{0}C. After stirring at 0 ^{o}C for 2 hours, the slurry was filtered. The filtrate was diluted with EtOAc, washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash chromatography (gradient, CH_2Cl_2/MeOH, 100:1 to 40:1) to afford compound **51** (2.75 g, 64% yield) as a yellow solid.

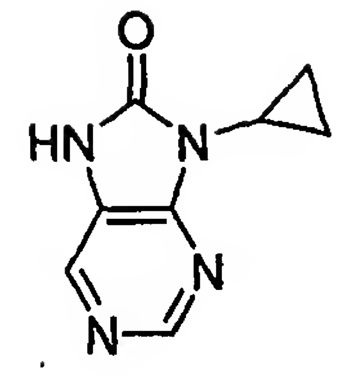
^{1}H NMR (DMSO-d_6) δ 0.61-0.64 (m, 2 H), 0.74-0.78 (m, 2 H), 2.92 (bs, 1 H), 8.43 (bs, 1 H), 8.51 (s, 1 H);
MS m/e 215 (MH^+).



52

Pyrimidine **51** was reduced using catalytic hydrogenation with 10 % palladium on carbon in MeOH at 40 psi (Parr shaker) for 1 hour to afford compound **52**.

^{1}H NMR (DMSO-d_6) δ 0.74-0.76 (m, 2 H), 0.79-0.83 (m, 2 H), 3.06-3.11 (m, 1 H), 6.17 (bs, 2 H), 7.47 (d, J = 1.5 Hz, 1 H), 8.37 (d, J = 1.0 Hz, 1 H), 9.09 (d, J = 3.8 Hz, 1 H);
MS m/e 151 (MH^+).

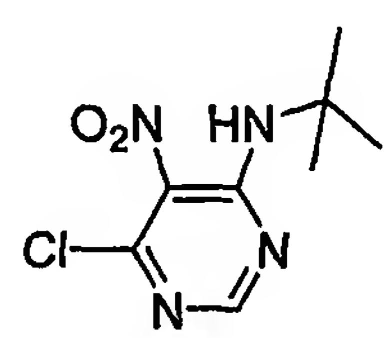


53

Compound **53** was obtained by cyclization of diamine **52** according to the same procedure described for compound **36** using phosgene and polyvinylpyridine.

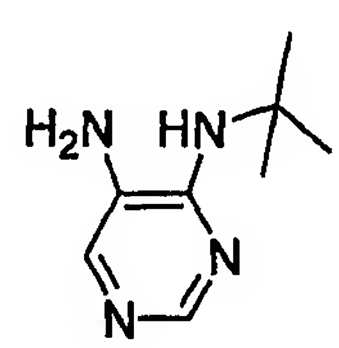
^{1}H NMR (CD_3OD) δ 1.14-1.19 (m, 2 H), 1.20-1.27 (m, 2 H), 3.11-3.18 (m, 1 H), 8.47 (d, J = 0.45 Hz, 1 H), 9.01 (s, 1 H);
MS m/e 177 (MH^+).

2-Oxo-imidazopyrimidine **56** was prepared using the same procedure for compound **53**, except that cyclopropylamine was replaced with *t*-butylamine. The compound was used as a crude intermediate for the coupling reaction without further purification.



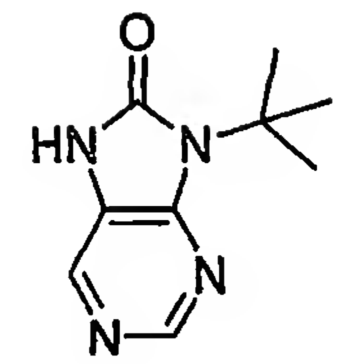
54

^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9 H), 7.26 (bs, 1 H), 8.37 (s, 1 H);
MS m/e 231 (MH^+).



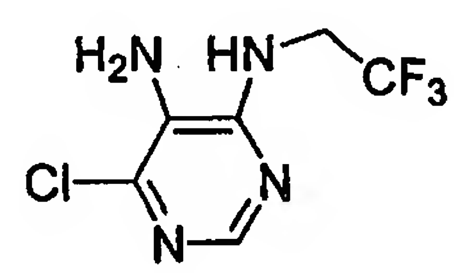
55

^{1}H NMR (CD_3OD) δ 1.57 (s, 9 H), 7.49 (d, J = 1.3 Hz, 1 H), 8.27 (d, J = 1.3 Hz, 1 H);
MS m/e 167 (MH^+).



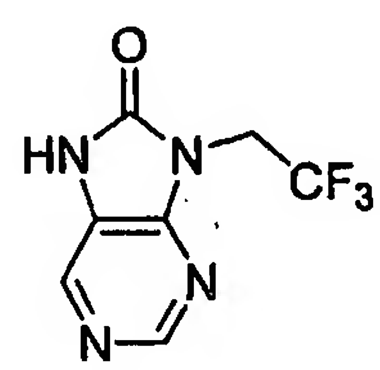
56

2-Oxo-imidazopyrimidine **58** was prepared according to the same procedure described for compound **53**, except that cyclopropylamine was replaced with 2,2,2-trifluoroethylamine. The crude intermediate was used in the coupling reaction without further purification.



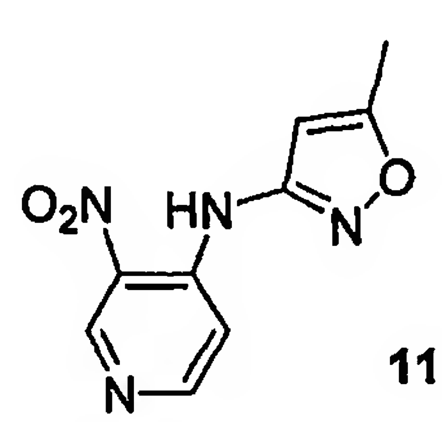
57

^{1}H NMR (CD_3OD) δ 4.30-4.36 (m, 2 H), 8.46 (s, 1 H);
MS m/e 226 (MH^+).



58

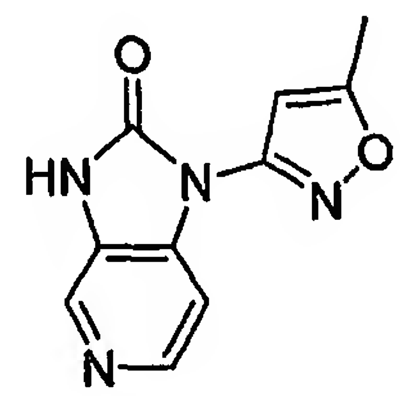
2-Oxo-imidazopyridine **113** was prepared according to the same procedure for the preparation of **36**, except that cyclopropylamine was replaced with 2 equivalents of 3-amino-5-methylisoxazole, and the reaction was carried out in MeOH at 100 °C for 18 hours in a sealed pressure tube.



112

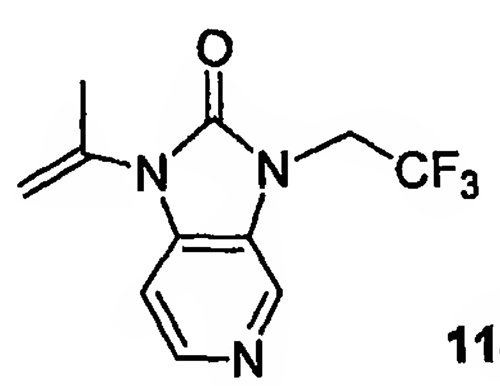
^{1}H NMR (CD_3OD) δ 0.88 (s, 3 H), 4.71 (s, 1 H), 6.79 (d, J = 6.2 Hz, 1 H), 6.95 (d, J = 6.2 Hz, 1 H), 7.69 (d, 1 H);
IR (KBr, cm^{-1}) 3323, 3125, 3097, 1604, 1581, 1521, 1499, 1228, 1179;
MS m/e 221 (MH^+);

Anal. Calcd for $C_9H_8N_4O_3$:		C, 49.09; H, 3.66; N, 25.44
	Found:	C, 49.04; H, 3.63; N, 25.06.



113

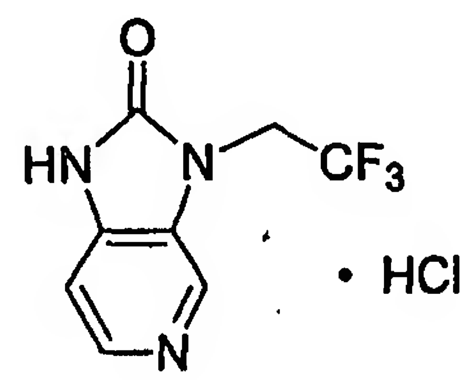
^{1}H NMR (CD_3OD) δ 2.50 (s, 3 H), 6.94 (s, 1 H), 7.95 (dd, J = 0.6, 6.55 Hz, 1 H), 8.31 (s, 1 H), 8.32 (d, J = 5.5 Hz, 1 H);
IR (KBr, cm^{-1}) 3546, 3463, 2679, 1744, 1720, 1596, 1474, 1457, 1193, 1129, 809, 633;
MS m/e 217 (MH^+).



114

A mixture of compound **26** (400 mg, 2.28 mmol) and BTPP (1.57 g, 5.02 mmol) in THF (10 mL) was stirred for 20 minutes after which 2,2,2-trifluoroethyl *p*-toluenesulfonate (605 mg, 2.40 mmol) was added to the mixture. The reaction mixture was stirred at 45 °C for 18 hours and then at 60 °C for an additional 24 hours. The solvent was evaporated and the residue was diluted with H_2O and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and evaporated. Purification by flash column chromatography (EtOAc/MeOH, 20:1) gave 295 mg (50% yield) of **114** as a white solid.

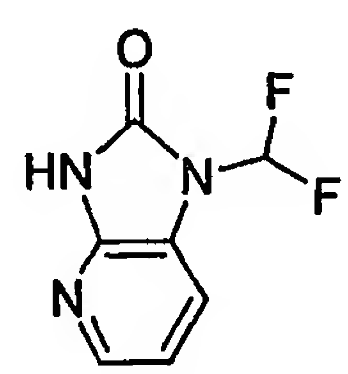
^1H NMR ($CDCl_3$) δ 2.24 (s, 3 H), 4.51 (q, J = 8.6 Hz, 2 H), 5.24 (s, 1 H), 5.43 (d, J = 1.1 Hz, 1 H), 7.10 (d, J = 5.5 Hz, 1 H), 8.39 (s, 1 H), 8.40 (d, J = 5.5 Hz, 1 H);
IR (KBr, cm^{-1}) 3026, 1727, 1605, 1503, 1169, 1156, 1126, 827;
MS m/e 258 (MH^+).



115

Compound **114** (272 mg, 1.06 mmol) and concentrated HCl (12 mL) in MeOH (20 mL) were refluxed for 72 hours. The solvent was evaporated and the residue was dried under vacuum to give 263 mg (99% yield) of compound **115** as the HCl salt.

^1H NMR (DMSO-d_6) δ 4.93 (q, J = 9.2 Hz, 2 H), 7.61 (d, J = 6.3 Hz, 1 H), 8.54 (d, J = 6.3 Hz, 1 H), 8.89 (s, 1 H);
MS m/e 218 (MH^+).



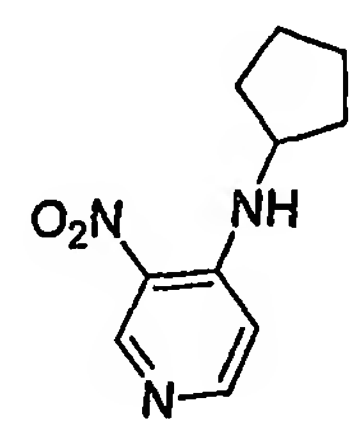
116

Compound **28B** (1.2 g, 6.86 mmol) and BTPP (3.21 g, 10.28 mmol) in CH_2Cl_2 were mixed together in a sealed flask and cooled to –78 °C. Chlorodifluoromethane (gas, approximately 2 g, 23.26 mmol) was bubbled into the solution in the sealed flask. The flask was sealed and the temperature was raised to 0 °C for 10 minutes and then to room temperature for 3 minutes. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and evaporated. To the residue was added 6 N HCl in MeOH (1:1 mixture, 10 mL). The mixture was stirred at reflux for 6 hours. The reaction was neutralized with solid Na_2CO_3. The solvent was

concentrated and the resulting aqueous solution was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and evaporated. Purification by flash column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 5:1) gave 398 mg (31% yield) of **116**.

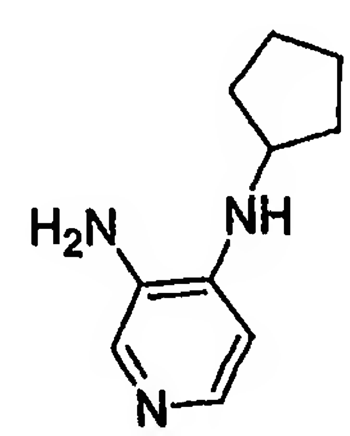
^{1}H NMR ($CDCl_3$) δ 7.14 (dd, J = 5.7, 7.4 Hz, 1 H), 7.36 (t, J =58.7 Hz, 1 H), 7.62 (d, J = 7.8 Hz, 1 H), 8.21 (d, J = 5.3 Hz, 1 H), 9.40 (bs, 1 H);
MS m/e 186 (MH^+).

Compound **119** was prepared using the same procedure described for the preparation of **36**, except that cyclopropylamine was replaced with 2 equivalents of cyclopentylamine, and the reaction was carried out in a sealed pressure tube at 120 °C for 2 hours.



117

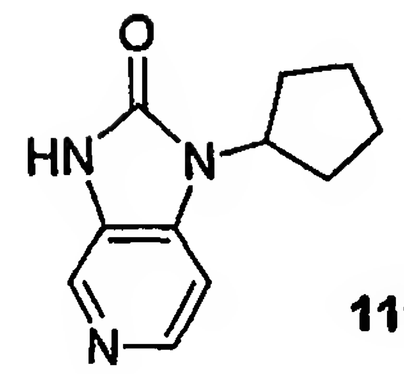
^{1}H NMR ($CDCl_3$) δ 1.62-1.69 (m, 2 H), 1.70-1.76 (m, 2 H), 1.79-1.85 (m, 2 H), 2.10-2.16 (m, 2 H), 3.96-4.01 (m, 1 H), 6.76 (d, J = 6.2 Hz, 1 H), 8.23 (bs, 1 H), 8.27 (d, J = 6.2 Hz, 1 H), 9.21 (s, 1 H);
MS m/e 208 (MH^+).



118

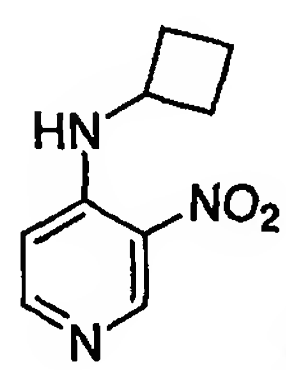
^{1}H NMR ($CDCl_3$) δ 1.48-1.53 (m, 2 H), 1.61-1.64 (m, 2 H), 1.69-1.74 (m, 2 H), 2.00-2.06 (m, 2 H), 3.12 (bs, 2 H), 3.77-3.83 (m, 1 H), 4.22 (bd, J = 4.5 Hz, 1 H), 6.47 (d, J = 5.4 Hz, 1 H), 7.85 (s, 1 H), 7.92 (d, J = 5.4 Hz, 1 H);

MS m/e 178 (MH^+).

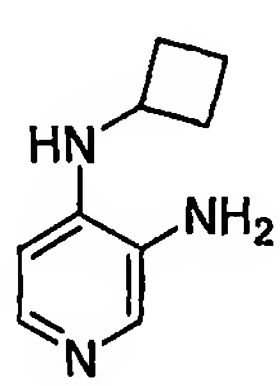

119

^{1}H NMR (DMSO-d_6) δ 1.61-1.68 (m, 2 H), 1.85-1.95 (m, 4 H), 1.97-2.02 (m, 2 H), 4.11 (bs, 1 H), 4.67-4.74 (m, 1 H), 7.20 (d, J = 5.3 Hz, 1 H), 8.16 (d, J = 5.4 Hz, 1 H), 8.19 (s, 1 H);
MS m/e 204 (MH^+).

Compound **122** was prepared using the same procedure described for the preparation of **36**, except that cyclopropylamine was replaced with 2 equivalents of cyclobutylamine, and the reaction was carried out in a sealed pressure tube at 100 °C.

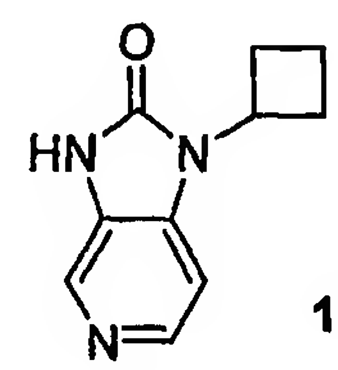

120

^{1}H NMR ($CDCl_3$) δ 1.89-1.97 (m, 2 H), 2.05-2.09 (m, 2 H), 2.50-2.56 (m, 2 H), 4.06-4.13 (m, 1 H), 6.56-6.62 (m, 1 H), 8.23 (s, 1 H), 8.27 (d, J=5.6 Hz, 1 H), 9,21 (s, 1 H);
MS m/e 194 (MH^+).


121

^{1}H NMR (DMSO-d_6) δ 1.70-1.79 (m, 2 H), 1.83-1.91 (m, 2 H), 2.32-2.50 (m, 2 H), 3.85-3.91 (m, 1 H), 4.59 (s, 2 H), 5.49 (d, J=6.2 Hz, 1H), 6.22 (d, J=5.3 Hz, 1 H), 7.55 (d, J= 5.2 Hz, 1 H), 7.63 (s, 1 H);

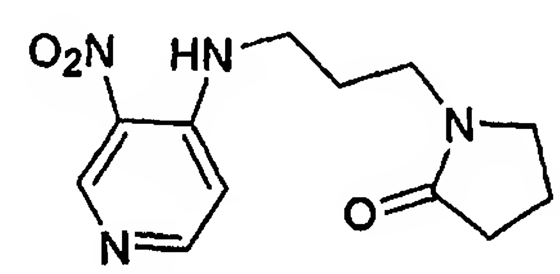
MS m/e 164 (MH^+).



122

^{1}H NMR (CD_3OD) δ 1.92-2.04 (m, 2 H), 2.43-2.49 (m, 2 H), 2.88-2.97 (m, 2 H), 4.93-4.98 (m, 1 H), 7.83 (d, J= 6.6 Hz, 1 H), 8.41-8.43 (m, 2 H);

MS m/e 190 (MH^+).

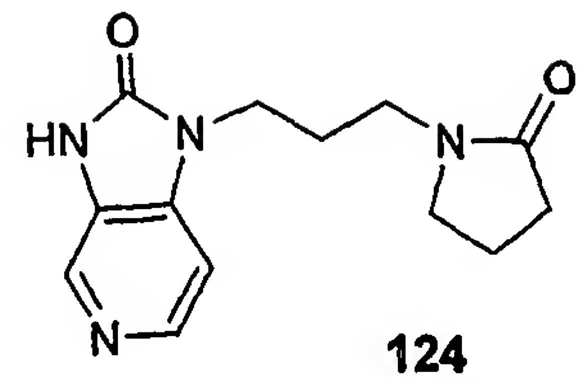


123

To a solution of 4-chloro-3-nitropyridine (4.9 g, 30.80 mmol) and 1-(3-aminopropyl)-2-pyrrolidinone (4.4 g, 30.80 mmol) in CH_3CN (50 mL) was added K_2CO_3 (4.25 g, 30.8 mmol) and the mixture was stirred for 8 hours. Additional 1-(3-aminopropyl)-2-pyrrolidinone (0.2 g, 1.41 mmol) was added and the mixture was stirred for 24 hours at room temperature. The mixture was filtered and concentrated to give 8.0 g (98% yield) of the compound **123** as an orange oil.

^{1}H NMR ($CDCl_3$) δ 1.89-1.99 (m, 2 H); 2.02-2.15 (m, 2 H), 2.35 (t, J = 8.05 Hz, 2 H); 3.36-3.47 (m, 6 H), 6.70 (d, J = 6.2 Hz, 1 H), 8.28 (d, J = 6.27 Hz, 1 H), 8.37-8.40 (s, 1 H), 9.20 (s, 1 H);

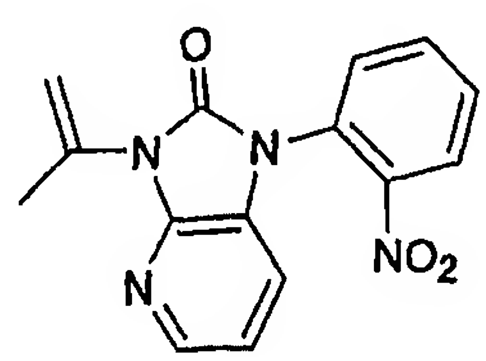
MS m/e 264 (MH^+).



124

A mixture of **123** (2.0 g, 7.6 mmol) and 10% palladium on carbon (200 mg) in EtOH (50 mL) was hydrogenated at 50 psi for 18 hours, filtered and concentrated to give 1.6 g (90% yield) of the diamine as a black oil. The oil was dissolved in CH_2Cl_2 (40 mL), treated with carbonyl diimidazole (1.22 mg, 7.5 mmol) and stirred for 12 hours at room temperature. The solvent was evaporated and the residue was subjected to flash column chromatography (gradient, 3% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to give 1.09 g (62% yield) of compound **124** as an orange gum.

^{1}H NMR ($CDCl_3$) δ 2.01-2.05 (m, 4 H), 2.39 (t, J = 7.9 Hz, 2 H) 3.37-3.43 (m, 4 H), 3.90 (t, J = 7.2 Hz, 2 H), 7.01 (d, J = 5.4 Hz, 1 H), 8.29 (d, J = 5.4 Hz, 1 H), 8.37 (s, 1 H);
MS m/e 260 (MH^+).

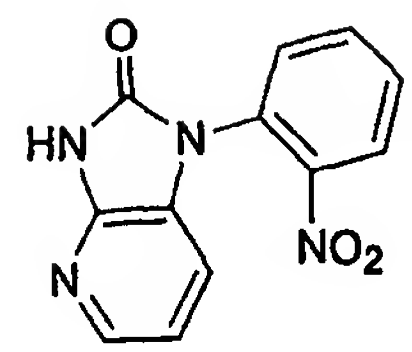


125

A mixture of **28A** (1.00 g, 5.71 mmol), *o*-fluoronitrobenzene (0.88 g, 6.28 mmol) and Cs_2CO_3 (5.58 g, 17.1 mmol) in DMF was stirred at room temperature for 12 hours. The reaction mixture was diluted with EtOAc and washed with water and brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (gradient, CH_2Cl_2/hexane, 40:1 to 20:1) gave 1.10 g (65% yield) of **125** as a yellow foam.

^{1}H NMR ($CDCl_3$) δ 2.28-2.32 (m, 3 H), 5.45-5.49 (m, 2 H), 7.01-7.05 (m, 1 H), 7.11-7.15 (m, 1 H), 7.62-7.68 (m, 2 H), 7.80-7.84 (m, 1 H), 8.14-8.22 (m, 2 H);

MS m/e 297 (MH^+).

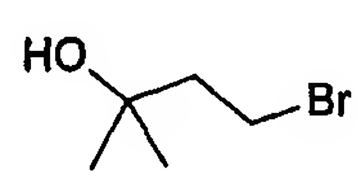


126

Compound **126** was prepared from compound **125** according to the same procedure described for compound **115**.

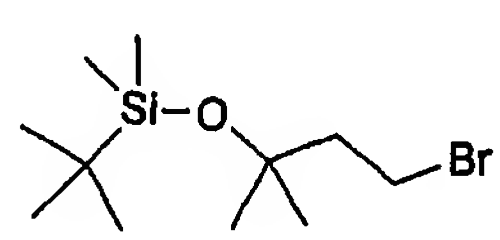
^{1}H NMR (DMSO-d_6) δ 7.06-7.09 (m, 1 H), 7.33-7.34 (m, 1 H), 7.75-7.79 (m, 1 H), 7.85-7.87 (m, 1 H), 7.94-7.98 (m, 1 H), 8.04-8.05 (m, 1 H), 8.21-8.23 (m, 1 H);
MS m/e 257 (MH^+).

III. Preparation of R_1-LGs:



127

Compound **127** was prepared according to the procedure described by A. Yebga et al. in *Eur. J. Med. Chem.*, **1995**, *30*, 769-777.



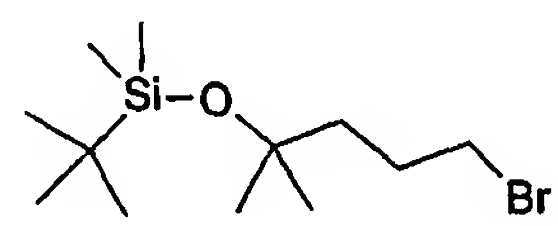
128

Compound **128** was prepared according to the procedure described by J. C. Heslin and C. J. Moody in *J. Chem. Soc. Perkins Trans. I*, **1988**, *6*, 1417-1423.

129

Compound **129** was prepared according to the same procedure described for compound **127**.

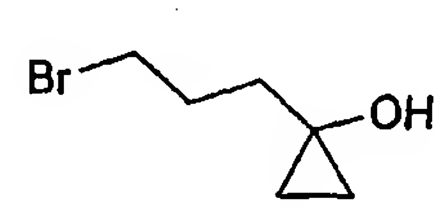
^{1}H NMR ($CDCl_3$) δ 1.22 (s, 6 H), 1.57-1.60 (m, 2 H), 1.92-1.98 (m, 3 H), 3.42 (t, J = 6.7 Hz, 2 H).



130

To neat 2,6-lutidine (11.42 g, 106.60 mmol) cooled with an ice bath to 0 °C was added *t*-butyldimethylsilyltrifluoromethane sulfonate (16.91 g, 63.96 mmol). After 30 minutes, a solution of compound **129** (7.72 g, 42.64 mmol) in CH_2Cl_2 (15 mL) was added. The resulting brown reaction mixture was stirred at 0 °C for 2.5 hours. The reaction mixture was poured onto ice (50 mL) and saturated aqueous sodium bicarbonate solution (50 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and evaporated. The crude brown oil was purified by flash column chromatography (pentane:Et_2O, 15:1) to give compound **130** as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6 H), 0.85 (s, 9 H), 1.21 (s, 6 H), 1.52-1.55 (m, 2 H), 1.93-1.99 (m, 2 H), 3.42 (t, J = 6.7 Hz, 2 H).

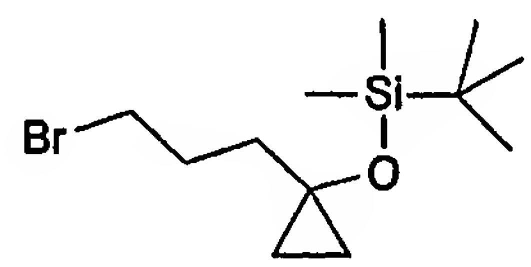


131

Compound **131** was prepared according to the procedure described by O. Kulinkovich et al. in *Tetrahedron Letters*, **1996**, *37*, 1095-1096. To a solution of ethyl-4-bromobutyrate (16.36 g, 83.85 mmol) in Et_2O (200 mL) was added titanium (IV) isopropoxide (2.38 g, 8.39 mmol). Ethylmagnesium bromide (3.0 M in Et_2O, 58.7 mL, 176.09 mmol) was added to the mixture slowly via addition funnel over 30 minutes maintaining the temperature between 10-20 °C. The reaction mixture was stirred for 6 hours at room temperature and then poured

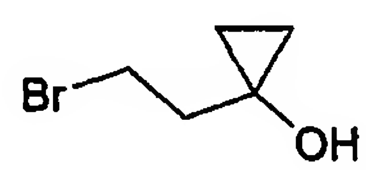
slowly into chilled 10% aqueous H_2SO_4 (300 mL) and stirred. The layers were separated and the aqueous layer was further extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and evaporated. The crude oil was purified by flash column chromatography (gradient, hexanes/Et_2O 3:1 to 1:1) to give 10.3g (67% yield) of compound **131** as a yellow oil.

^{1}H NMR ($CDCl_3$) δ 0.42-0.48 (m, 2 H), 0.69-0.76 (m, 2 H), 1.63-1.70 (m, 2 H), 2.05-2.14 (m, 2 H), 3.45-3.50 (m, 2 H);



132

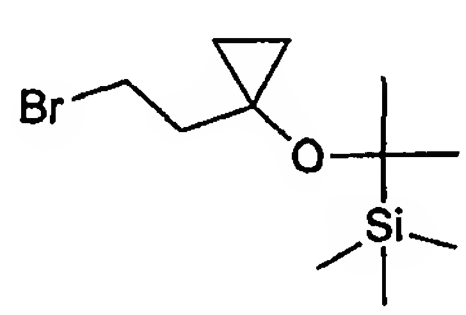
Compound **132** was prepared from compound **131** according to the same procedure described for compound **130** and was used immediately for coupling upon isolation.



133

Compound **133** was prepared according to the same procedure described for compound **131** using ethyl 3-bromopropionate.

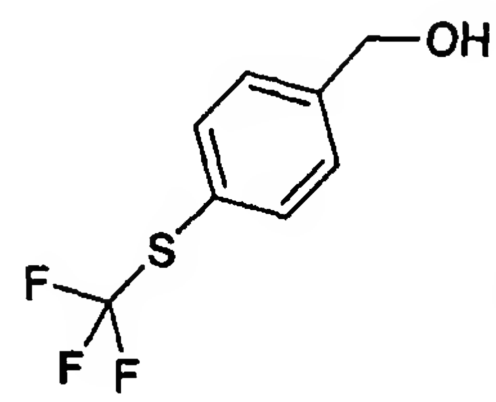
^{1}H NMR ($CDCl_3$) δ 0.51 (t, J = 6.1 Hz, 2 H), 0.76 (t, J = 6.2 Hz, 2 H), 2.07 (t, J = 7.3 Hz, 2 H), 3.57 (t, J = 7.3 Hz, 2 H).



134

Compound **134** was prepared from compound **133** according to the same procedure described for compound **130**.

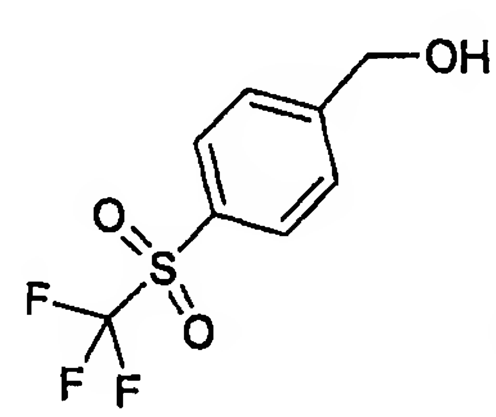
^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.50 (t, J = 6.3 Hz, 2 H), 0.74 (t, J = 6.3 Hz, 2 H), 0.85 (s, 9 H), 2.03 (t, J = 8.0 Hz, 2 H), 3.56 (t, J = 8.0 Hz, 2 H).



135

A solution of 4-(trifluoromethylthio) benzoic acid (5.00 g, 22.50 mmol) and triethylamine (2.36g, 23.40 mmol) in THF (50 mL) was cooled to 0 °C and to the solution was added ethyl chloroformate (2.53 g, 23.40 mmol). The mixture was filtered and the added dropwise to a cooled solution of sodium borohydride (3.54 g, 93.38 mmol) in a mixture of H_2O and THF (1:1 ratio, 50 mL). The reaction mixture was stirred for 2 hours keeping the temperature below 15 °C and then for 18 hours at room temperature. The reaction was quenched with 1N HCl and the organic layer was separated. The aqueous layer was extracted with Et_2O and all organic layers were combined, dried over Na_2SO_4, and evaporated. The resulting solid was dissolved in EtOAc and was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated to give 3.53 g (75% yield) of compound **135** as a white solid.

^{1}H NMR (DMSO-d_6) δ 4.57 (d, J = 5.7 Hz, 2 H), 5.38 (t, J = 5.7 Hz, 1 H), 7.48 (d, J = 7.3 Hz, 2 H), 7.68 (d, J = 7.3 Hz, 1 H).

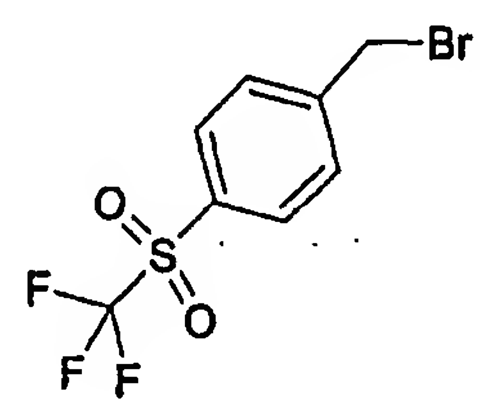


136

A mixture of compound **135** (3.50 g, 16.81 mmol), hydrogen peroxide (30%, 19.05 g, 168.10 mmol) and glacial acetic acid (40 mL) was stirred at 80 °C

for several minutes and then at 50 °C for 48 hours. The solution was poured into H_2O and extracted with Et_2O. The combined extracts were washed with aqueous 10% $NaHCO_3$, dried over Na_2SO_2, and evaporated to give 3.6 g (89% yield) of compound **136** as a white solid.

^1H NMR (DMSO-d_6) δ 4.70 (d, J = 7.1 Hz, 2 H), 5.61 (bs, 1 H), 7.78 (d, J = 7.2 Hz, 2 H), 8.10 (d, J = 7.2 Hz, 2 H).



137

A solution of alcohol **136** (2.0 g, 8.32 mmol) in Et_2O (50 mL) was cooled to –5 °C with an ice/salt bath. To this solution was added phosphorous tribromide and the resulting mixture was stirred at –5 °C for 5 hours and then at room temperature for 18 hours. The reaction mixture was poured into ice water and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over Na_2SO_4, and evaporated to give 1.45 g (56% yield) of **137** as a clear oil.

^1H NMR (DMSO-d_6) δ 4.87 (s, 2 H), 7.91 (d, J = 8.5 Hz, 2 H), 8.15 (d, J = 8.4 Hz, 2 H).

IV. Preparation of Examples of Formula I:

Unless a specific procedure is described, Examples **1-166** are prepared according to the general coupling procedures described below:

General Coupling Procedure of 2-Chloromethyl-benzimidazoles (II) and 2-Oxo-imidazopyridines or 2-Oxo-imidazopyrimidines in Scheme I-A.

Examples **1-3, 8-12, 14-16, 23-46, 65, 69-70, 72, 90, 94, 102, 104, 111-113, 120, 122, 126, 128-131, 135-136, 140-151, 156-157, 154-155, 157** and **160-163**, and **166** were prepared according to the following procedure:

To a solution of **II** and 2-oxo-imidazopyridine or 2-oxo-imidazopyrimidine (1 equivalent of each) in THF or CH_2Cl_2 or DMF is added 3-4 equivalents of BTPP or Cs_2CO_3. The mixture is stirred at 0 °C or room temperature for 1-16 hours. The solvent is evaporated, and the residue is diluted with water and extracted with EtOAc. The crude product is then purified by chromatography on silica gel or by reverse phase preparative HPLC.

General Procedure of Reacting Ia with R_2-LG in Scheme I-B.

Examples **5-7, 18, 100, and 138** were prepared according to the following procedure:

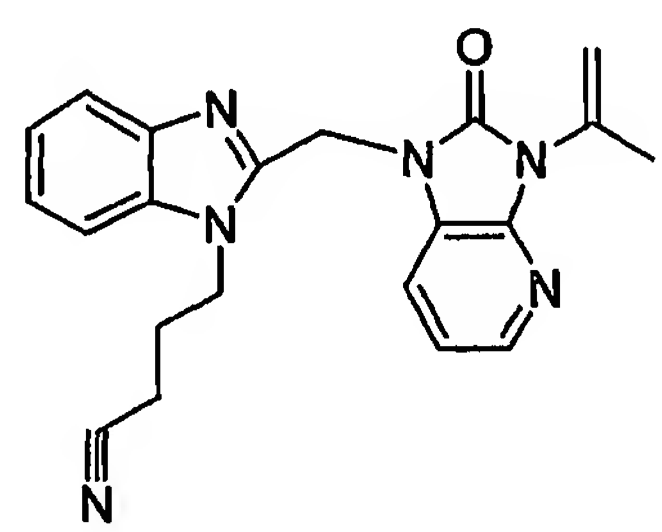
To a solution of **Ia** and 1.5-3 equivalents of BTPP, Cs_2CO_3, or BEMP on polystyrene resin in THF or DMF is slowly added R_2-LG at room temperature. When the reaction is completed, the solvent is evaporated or resin is filtered and filtrate is evaporated. The residue is purified by dissolving in EtOAc or CH_2Cl_2 and washing with water followed by flash chromatography, or by trituration of the solid collected from the reaction in solvents such as MeOH, or by reverse phase preparative HPLC.

General Procedure of Reacting V with R_1-LG in Scheme I-C.

Examples **48, 67-68, 76, 78, 80, 82, 84, 88, 124,** and **152-153** were prepared according to the following procedure.

To a mixture of V and 1.5-3 equivalents of sodium hydride or BEMP on polystryrene resin in THF, DMF or CH_3CN is added R_1-LG. The reaction is stirred at temperatures ranging from 0 °C to 80 °C for 30 minutes to 18 hours. In examples where BEMP on poylstyrene resin is utilized, the resin is filtered. The filtrate is evaporated and the residue is purified by flash column chromatography on silica or reverse phase preperative HPLC. In examples where sodium hydride is used as base, the reaction mixture is diluted with water, extracted with EtOAc or CH_2Cl_2, and purified by flash column chromatography on silica or reverse phase preparative HPLC.

Example 1



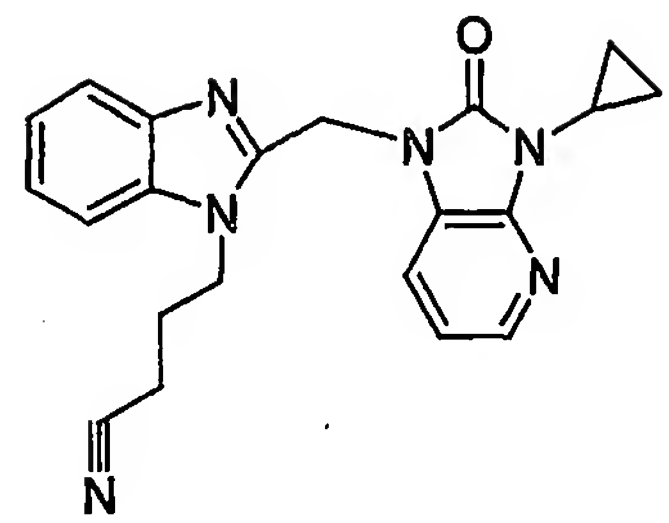
^{1}H NMR ($CDCl_3$) δ 2.05-2.11 (m, 2 H), 2.29 (s, 3 H), 2.50 (t, J = 7.1 Hz, 2 H), 4.58 (t, J = 7.6 Hz, 2 H), 5.36 (s, 1 H), 5.48 (s, 3 H), 7.06 (dd, J = 5.2, 7.8 Hz, 1 H), 7.35-7.45 (m, 3 H), 7.84 (d, J = 7.4 Hz, 1 H), 7.94 (bd, J = 6.4 Hz, 1 H), 8.08 (dd, J = 1.2, 5.2 Hz, 1 H);

IR (KBr, cm^{-1}) 3423, 2952, 2243, 1698, 1656, 1618, 1452, 1403, 1336, 1247, 1152, 790, 766, 743;

MS m/e 373 (MH^+);

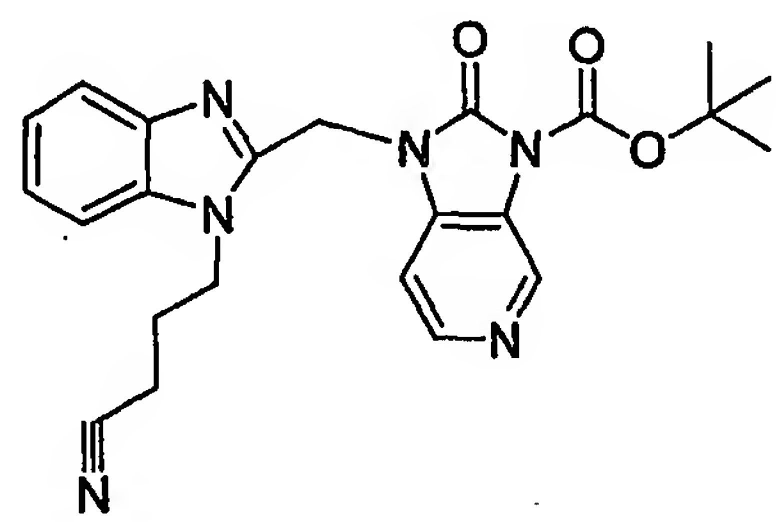
Anal. Calcd for $C_{21}H_{20}N_6O$:	C, 67.73; H, 5.41; N, 22.57
Found:	C, 67.35; H, 5.35; N, 22.41.

Example 2



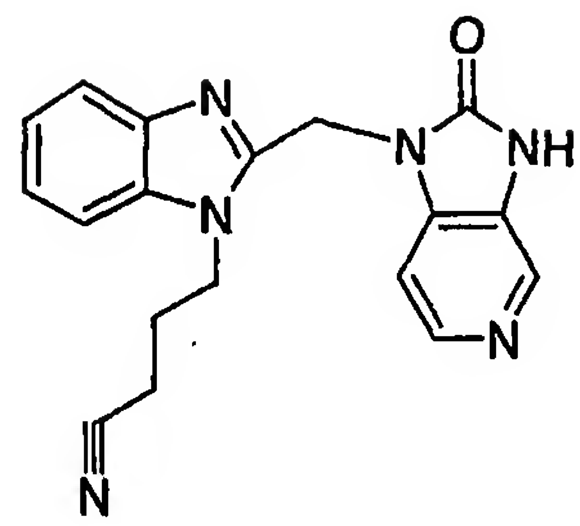
^{1}H NMR ($CDCl_3$) δ 1.13-1.21 (m, 4 H), 2.06-2.12 (m, 2 H), 2.51 (t, J = 7.2 Hz, 2 H), 3.01-3.05 (m, 1 H), 4.57 (t, J = 7.5 Hz, 2 H), 5.42 (s, 2 H), 7.01-7.05 (m, 1 H), 7.34-7.47 (m, 3 H), 7.81-7.86 (m, 2 H), 8.10 (d, J = 4.8 Hz, 1 H);
IR (KBr, cm^{-1}) 3424, 2244, 1702, 1333, 1474, 1461, 1280, 1164, 789;
MS m/e 373 (MH^+).

Example 3



^{1}H NMR (CD_3OD) δ 1.68 (s, 9 H), 2.18-2.21 (m, 2 H), 2.60 (t, J = 7.2 Hz, 2 H), 4.50 (t, J = 7.6 Hz, 2 H), 5.48 (s, 2 H), 7.23-7.25 (m, 1 H), 7.30 (t, J = 7.2 Hz, 1 H), 7.35 (d, J = 5.4 Hz, 1 H), 7.54 (d, J = 8.0 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 8.31 (d, J = 5.4 Hz, 1 H), 8.88 (s, 1 H);
MS m/e 433 (MH^+).

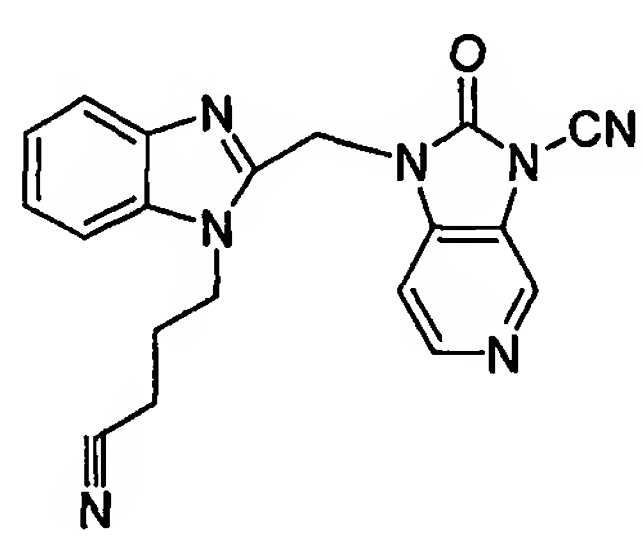
Example 4



The *t*-butoxycarbonyl group of Example **4** was removed by treating with aqueous 1 N NaOH solution using the procedure described for the preparation of intermediate compound **43**.

^{1}H NMR (CD_3OD) δ 2.05-2.11 (m, 2 H), 2.63 (t, J = 7.4 Hz, 2 H), 4.41 (t, J = 7.5 Hz, 2 H), 5.39 (s, 2 H), 7.16-7.19 (m, 1 H), 7.24-7.27 (m, 2 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 8.17 (d, J = 5.2 Hz, 1 H), 8.25 (s, 1 H), 11.34 (s, 1 H);
MS m/e 333 (MH^+).

Example 5

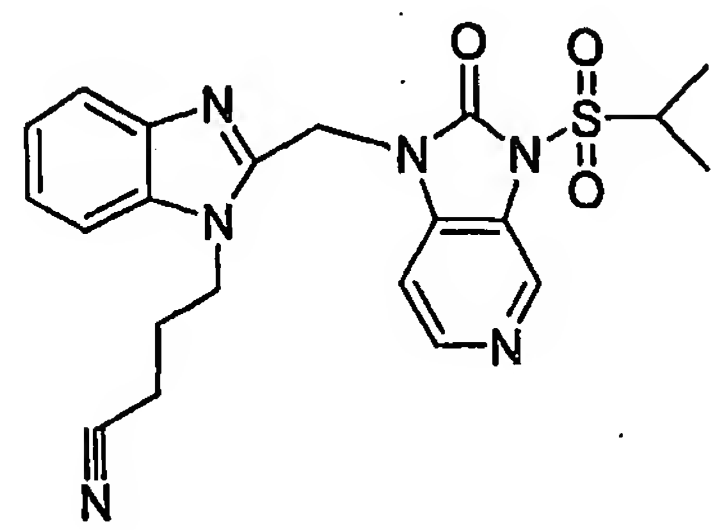


^{1}H NMR (DMSO-d_6) δ 2.14-2.17 (m, 2 H), 2.65 (t, J = 7.4 Hz, 2 H), 4.41 (t, J = 7.5 Hz, 2 H), 5.52 (s, 2 H), 7.18 (t, J = 8.0Hz, 1 H), 7.28 (t, J = 8.0 Hz, 1 H), 7.51 (d, J = 5.3 Hz, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 8.2 Hz, 1 H), 8.47 (d, J = 5.3 Hz, 1 H), 8.65 (s, 1 H);
IR (KBr, cm^{-1}) 3436, 2987, 2263, 1760, 1608, 1384, 1125, 748;
MS m/e 358 (MH^+);

Anal. Calcd for $C_{19}H_{15}N_7O \bullet 0.6EtOAc$: C, 62.65; H, 4.87; N, 23.90

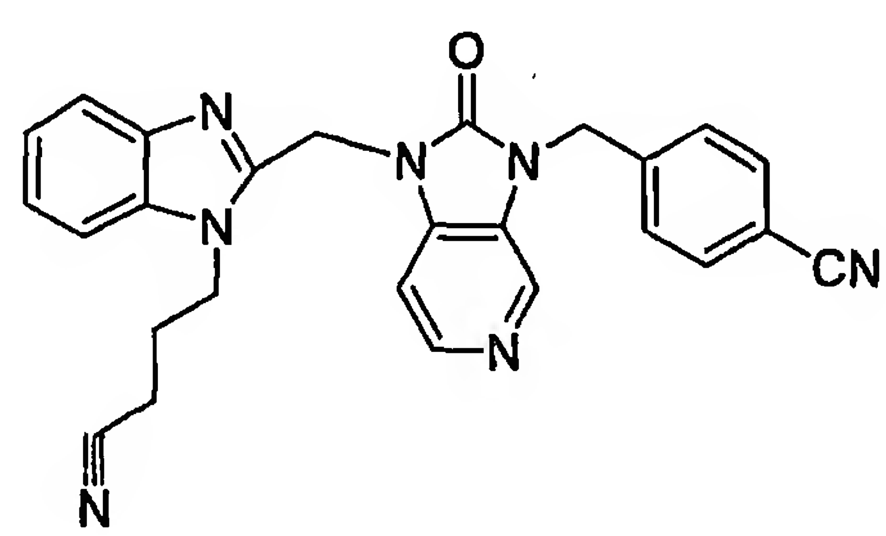
Found: C, 62.33; H, 4.76; N, 24.14.

Example 6



^{1}H NMR (CD_3OD) δ 1.53 (d, J = 6.8 Hz, 6 H), 2.27-2.32 (m, 2 H), 2.65 (t, J = 7.2 Hz, 2 H), 4.08-4.12 (m, 1 H), 4.57 (t, J = 7.5 Hz, 2 H), 5.68 (s, 2 H), 7.30 (t, J = 7.3 Hz, 1 H), 7.39 (t, J = 7.2 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.67 (d, J = 8.2 Hz, 1 H), 7.88 (d, J = 6.3 Hz, 2 H), 8.61 (d, J = 6.3 Hz, 1 H), 8.94 (s, 1 H);
IR (KBr, cm^{-1}) 3420, 2314, 2251, 2075, 2008, 1752, 1623, 1509, 1369, 1180, 738;
HRMS m/e 439.1552 (MH^+).

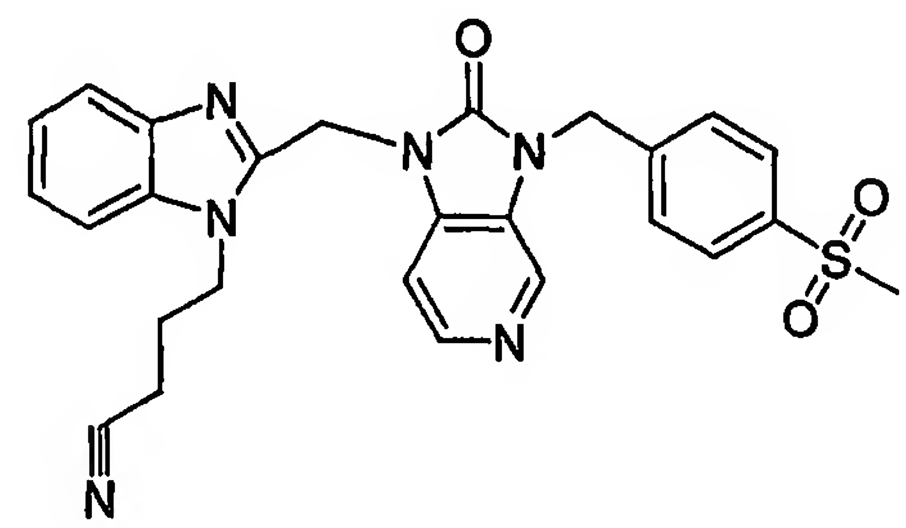
Example 7



^{1}H NMR (DMSO-d_6) δ 2.11-2.12 (m, 2 H), 2.63 (t, J = 7.4 Hz, 2 H), 4.42 (t, J = 7.4 Hz, 2 H), 5.28 (s, 2 H), 5.50 (s, 2 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.26 (t, J = 8.0 Hz, 1 H), 7.35 (d, J = 5.3 Hz, 1 H), 7.55-7.57 (m, 3 H), 7.62 (d, J = 8.1 Hz, 1 H), 7.86 (d, J = 8.2 Hz), 8.24 (d, J =5 .2 Hz, 1H), 8.40 (s, 1 H);
IR (KBr, cm^{-1}) 3424, 2953, 2250, 2229, 1716, 1609, 1503, 825, 744;
MS m/e 448 (MH^+);

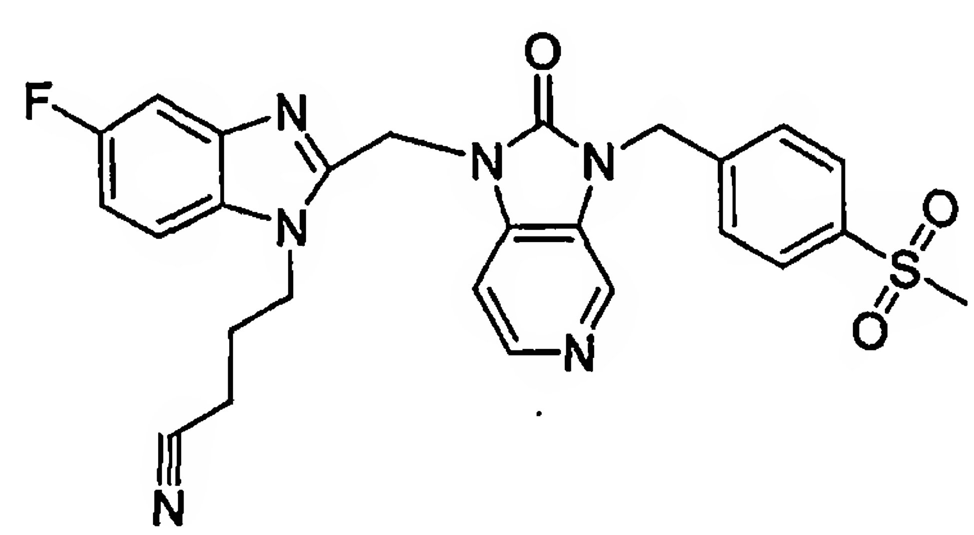
Anal. Calcd for $C_{26}H_{21}N_7O \bullet 0.25H_2O$: C, 69.09; H, 4.79; N, 21.69
Found: C, 69.00; H, 4.81; N, 21.77.

Example 8



^{1}H NMR (DMSO-d_6) δ 2.10-2.13 (m, 2 H), 2.64 (t, J = 7.4 Hz, 2 H), 3.20 (s, 3 H), 4.43 (t, J = 7.4 Hz, 2 H), 5.30 (s, 2 H), 5.51 (s, 2 H), 7.19 (t, J = 8.0 Hz, 1 H), 7.27 (t, J = 7.2 Hz, 1 H), 7.35 (d, J = 5.2 Hz, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.62-7.65 (m, 3 H), 7.93 (d, J = 8.3 Hz, 2 H), 8.24 (d, J = 5.2 Hz, 1 H), 8.43 (s, 1 H);
IR (KBr, cm^{-1}) 3424, 2246, 1707, 1614, 1501, 1407, 1306, 1148;
MS m/e 501 (MH^+);
Anal. Calcd for $C_{26}H_{24}N_6O_3S$: C, 62.38; H, 4.83; N, 16.78
Found: C, 62.31; H, 4.73; N, 16.75.

Example 9



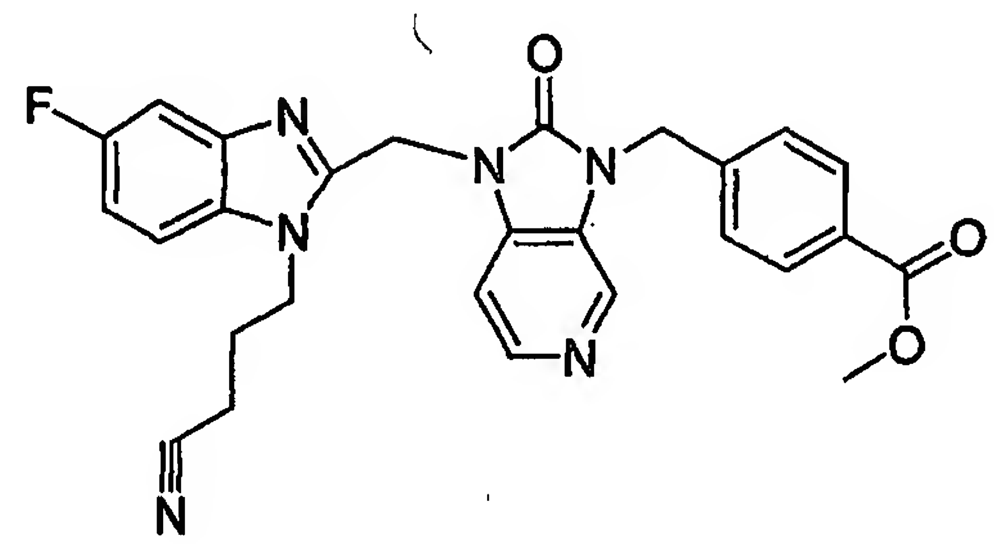
^{1}H NMR (DMSO-d_6) δ 2.11-2.14 (m, 2 H), 2.65 (t, J = 7.4 Hz, 2 H), 3.21 (s, 3 H), 4.44 (t, J = 7.4 Hz, 2 H), 5.30 (s, 2 H), 5.51 (s, 2 H), 7.16 (m, 1 H), 7.36 (d, J = 5.2 Hz, 1 H), 7.40 (q, J = 2.4, 9.7 Hz, 1 H), 7.63-7.68 (m, 3 H), 7.94 (d, J = 8.4 Hz, 2 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.44 (s, 1 H);

IR (KBr, cm^{-1}) 3423, 2926, 2248, 1707, 1613, 1602, 1148;

MS m/e 519 (MH^+);

Anal. Calcd for $C_{26}H_{23}FN_6O_3S$:		C, 60.22; H, 4.47, N, 16.20
	Found	C, 60.06; H, 4.69, N, 16.21.

Example 10



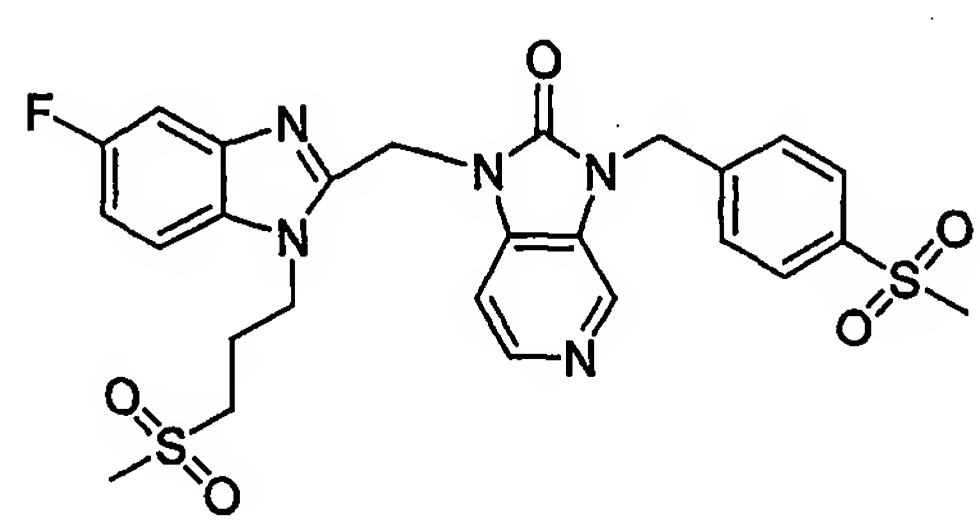
^{1}H NMR (DMSO-d_6) δ 2.09-2.13 (m, 2 H), 2.64 (t, J = 7.4 Hz, 2 H), 3.84 (s, 3 H), 4.43 (t, J = 7.4 Hz, 2 H), 5.26 (s, 2 H), 5.50 (s, 2 H), 7.13-7.17 (m, 1 H), 7.34-7.40 (m, 2 H), 7.51 (d, J = 8.3 Hz, 2 H), 7.64-7.67 (m, 1 H), 7.96-7.97 (m, 2 H), 8.23 (d, J = 5.2 Hz, 1 H), 8.39 (s, 1H);

IR (KBr, cm^{-1}) 3432, 2954, 2245, 1719, 1698, 1499, 1284, 1139;

MS m/e 499 (MH^+);

Anal. Calcd for $C_{21}H_{23}FN_6O_3$:		C, 65.05; H, 4.65; N, 16.85
	Found:	C, 65.25; H, 4.65; N, 16.87.

Example 11



^{1}H NMR (DMSO-d_6) δ 2.17-2.23 (m, 2 H), 3.02 (s, 3 H), 3.20 (s, 3H), 3.26 (t, J = 8.0 Hz, 2 H), 4.51 (t, J = 7.7 Hz, 2 H), 5.29 (s, 2 H), 5.50 (s, 2 H), 7.16 (dt, J =

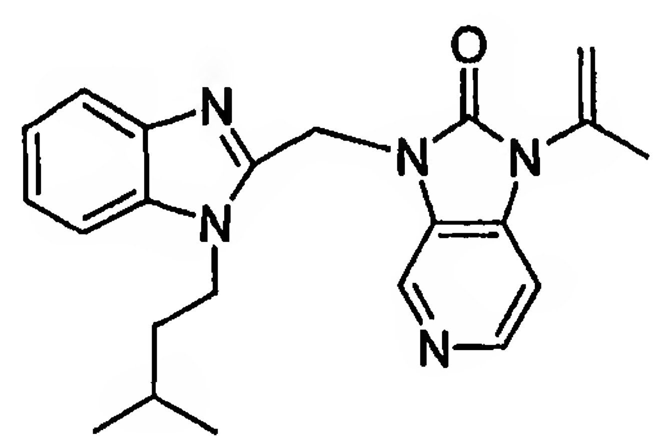
2.4, 9.2 Hz, 1 H), 7.36 (d, J = 4.9 Hz, 1 H), 7.40 (dd, J = 2.4, 9.5 Hz, 1 H), 7.63 (d, J = 8.2 Hz, 2 H), 7.68 (dd, J = 4.9, 8.9 Hz, 1 H), 7.93 (d, J = 8.3 Hz, 2 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.43 (s, 1 H);

IR (KBr, cm^{-1}) 3442, 2925, 2360, 1712, 1614, 1500, 1490, 1296, 1147, 761, 530;

MS m/e 572 (MH^+);

Anal. Calcd for $C_{26}H_{26}FN_5O_5S_2$:		C, 54.62; H, 4.58; N, 12.25
	Found:	C, 54.48; H, 4.69; N, 12.14.

Example 12



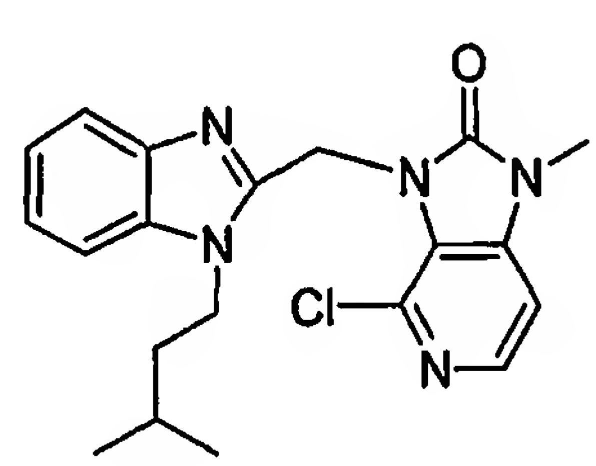
^{1}H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 0.95 (s, 3 H), 1.44-1.52 (m, 2 H), 1.60-1.73 (m, 1 H), 2.25 (s, 3 H), 4.28-4.33 (m, 2 H), 5.20 (s, 1 H), 5.41 (s, 3 H), 7.02 (d, J = 5.1 hz, 1 H), 7.27-7.31 (m, 3 H), 7.77-7.80 (m, 1 H), 8.31 (d, J = 5.1 Hz, 1 H), 8.73 (s, 1 H);

MS m/e 376 (MH^+);

IR (KBr, cm^{-1}) 2957, 1712, 1603, 1494, 1398, 1330, 1167, 1138, 816, 740;

Anal. Calcd for $C_{22}H_{25}N_5O$:		C, 70.38; H, 6.71; N, 18.65
	Found:	C, 70.24; H, 6.67; N, 18.71.

Example 13

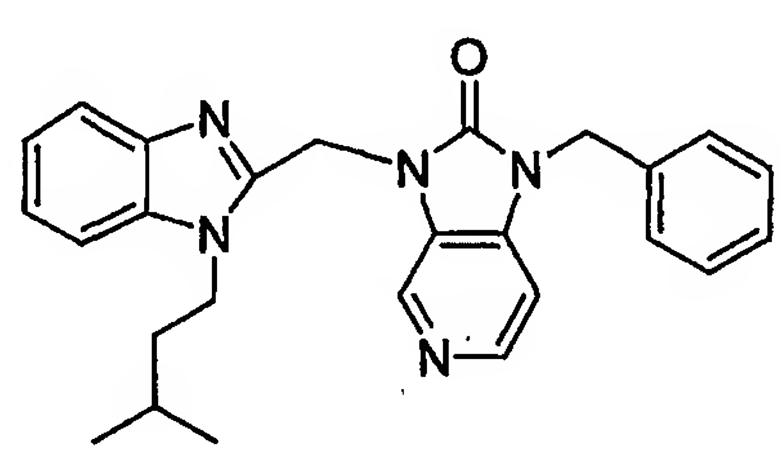


To a solution of 4-chloro-1-methyl-1,3-dihydro-imidazo[4,5 *c*]pyridin-2-one (Salor of Aldrich Chemical, 100 mg, 0.55 mmol) in DMF (10 mL) was added sodium hydride (26 mg, 60% dispersion in mineral oil) at room temperature. After stirring for 30 min, a neutral form of compound **4** (155 mg, 0.654 mmol) was added. The resulting mixture was stirred overnight and evaporated. The residue was diluted with water and extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, EtOAc, then EtOAc/MeOH, 20:1 to 10:1) to give the Example **13** (78 mg, 38% yield).

^1H NMR ($CDCl_3$) δ 1.07 (d, J = 6.3 Hz, 6 H), 1.72-1.86 (m, 3 H), 3.52 (s, 3 H), 4.27 (t, J = 7.7 Hz, 2 H), 5.64 (s, 2 H), 6.98 (d, J = 5.3 Hz, 1 H), 7.18-7.30 (m, 2 H), 7.35 (d, J = 7.5 Hz, 1 H), 7.66 (d, J = 7.4 Hz, 1 H), 8.13 (d, J = 5.3 Hz, 1 H); IR (KBr, cm^{-1}) 3449, 2954, 1735, 1613, 1586, 1503, 1441, 1133, 775;
MS m/e 384 (MH^+);

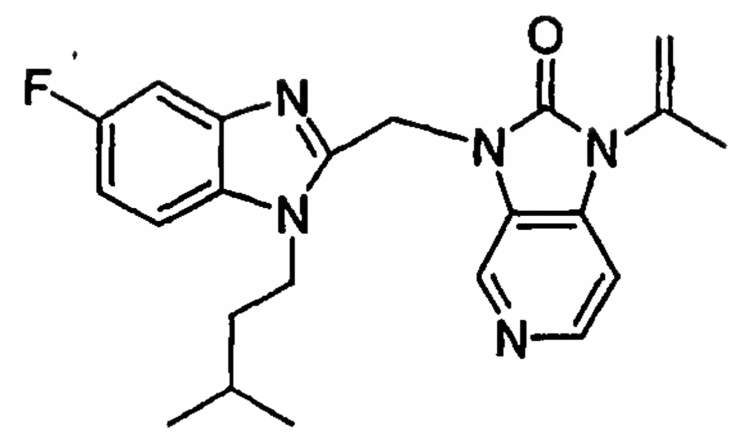
Anal. Calcd for $C_{20}H_{22}ClN_5O \bullet 1.10\ H_2O$:	C, 59.50; H, 6.04; N, 17.35
Found:	C, 59.46; H, 5.47; N, 16.68

Example 14



^1H NMR ($CDCl_3$) δ 1.07 (d, J = 6.1Hz, 6 H), 1.78-1.84 (m, 3 H), 4.42 (bt, J = 8.0 Hz, 2 H), 5.21 (s, 2 H), 5.77 (s, 2 H), 7.14 (d, J = 6.2 Hz, 1 H), 7.33-7.49 (m, 8 H), 7.94 (d, J = 8.0 Hz,1 H), 8.34 (d, J = 6.3 Hz, 1 H), 9.00 (s, 1 H);
MS m/e 376 (MH^+).

Example 15



^{1}H NMR (CD_3OD) δ 0.97 (d, J = 6.3 Hz, 6 H), 1.44-1.49 (m, 2 H), 1.62-1.73 (m, 1 H), 2.25 (s, 3 H), 4.27-4.33 (m, 2 H), 5.21 (s, 1 H), 5.38 (s, 2 H), 5.42 (s, 1 H), 7.02-7.08 (m, 2 H), 7.23 (dd, J = 4.5, 9.0 Hz, 1 H), 7.45 (dd, J = 2.4, 9.3 Hz, 1 H), 8.33 (d, J = 5.1 Hz, 1 H), 8.17 (s, 1 H);

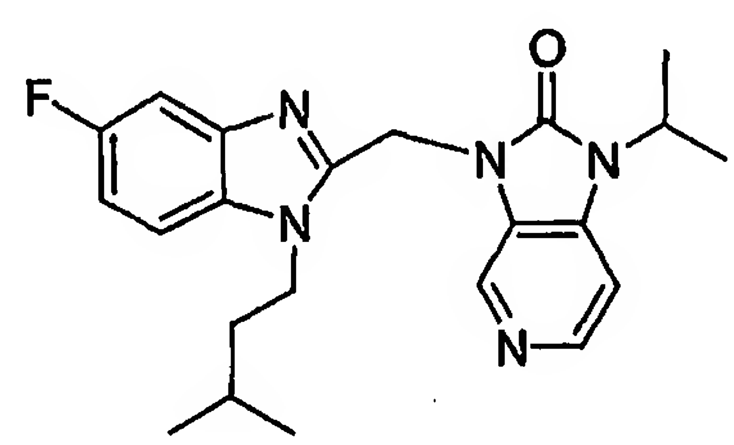
IR (KBr, cm^{-1}) 2960, 1713, 1605, 1495, 1455, 1399, 1333, 1163, 1140, 848, 813;

MS m/e 394 (MH^+);

Anal. Calcd for $C_{22}H_{24}FN_5O$: C, 67.16; H, 6.15; N, 17.80

Found: C, 67.25; H, 5.96; N, 17.88.

Example 16



^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.9 Hz, 6 H), 1.43-1.50 (m, 2 H), 1.55 (d, J = 7.2 Hz, 6 H), 1.55-1.75 (m, 1 H), 4.26-4.31 (m, 2 H), 4.70-4.80 (m, 1 H), 5.37 (s, 2 H), 7.01-7.08 (m, 2 H), 7.22 (dd, J = 4.8, 8.9 Hz, 1 H), 7.44 (dd, J = 2.7, 9.3 Hz, 1H), 8.29 (d, J = 5.4 Hz, 1 H), 8.68 (s, 1 H);

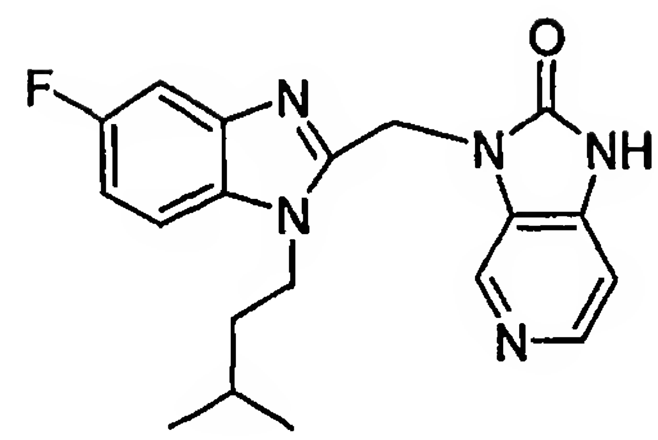
IR (KBr, cm^{-1}) 2956, 1706, 1493, 1456, 1389, 1332, 1133, 1113, 847;

MS m/e 396 (MH^+);

Anal. Calcd for $C_{22}H_{26}FN_5O \bullet 0.33H_2O$: C, 65.82; H, 6.69; N, 17.44

Found: C, 65.83; H, 6.30; N, 17.43.

Example 17

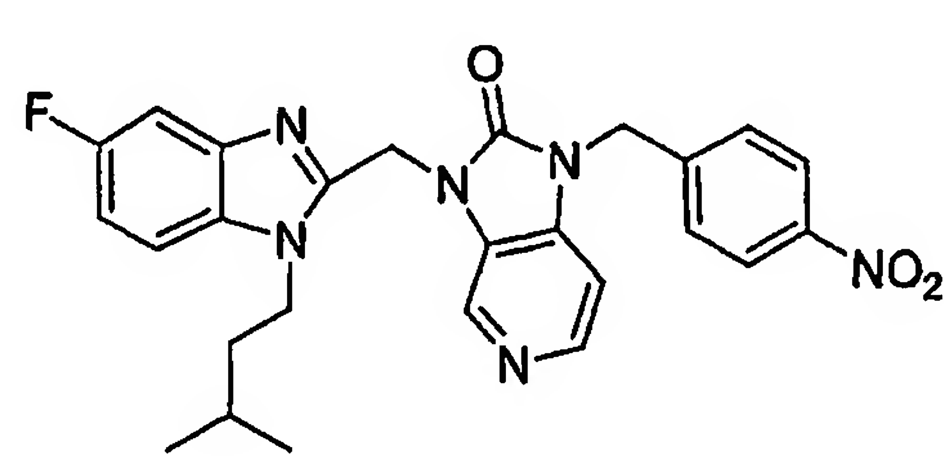


A solution of Example **15** (4.0 g, 10.17 mmol) in a mixture of MeOH (10 mL) and 6 N HCl (20 mL) was stirred at reflux overnight. The solution was cooled to room temperature and neutralized with concentrated NaOH solution, and evaporated. The residue was taken up with CH_2Cl_2, dried over $MgSO_4$, and evaporated. The residue was triturated with hot EtOAc and filtered to give Example **17** (3.22 g, 90% yield) as a white solid.

^{1}H NMR ($CDCl_3$) δ 0.99 (d, J = 6.6 Hz, 6 H), 1.50-1.55 (m, 2 H), 1.71-1.77 (m, 1 H), 4.25-4.31 (m, 2 H), 5.36 (s, 2 H), 6.97 (d, J = 5.1 Hz, 1 H), 7.06 (dt, J = 2.4, 9.3 Hz, 1 H), 7.23 (dd, J = 4.5, 8.7 Hz, 1 H), 7.43 (dd, J = 2.4, 9.3 Hz, 1 H), 8.29 (d, J = 5.1 Hz, 1 H), 8.62 (s, 1 H), 9.89 (bs, 1 H);
IR (KBr, cm^{-1}) 2958, 1720, 1622, 1491, 1455, 1139, 1014, 958, 894, 813;
MS m/e 375 (MH^+);

Anal. Calcd for $C_{19}H_{20}FN_5O$:	C, 64.58; H, 5.70; N, 19.82
Found:	C, 64.26; H, 5.58; N, 19.85.

Example 18



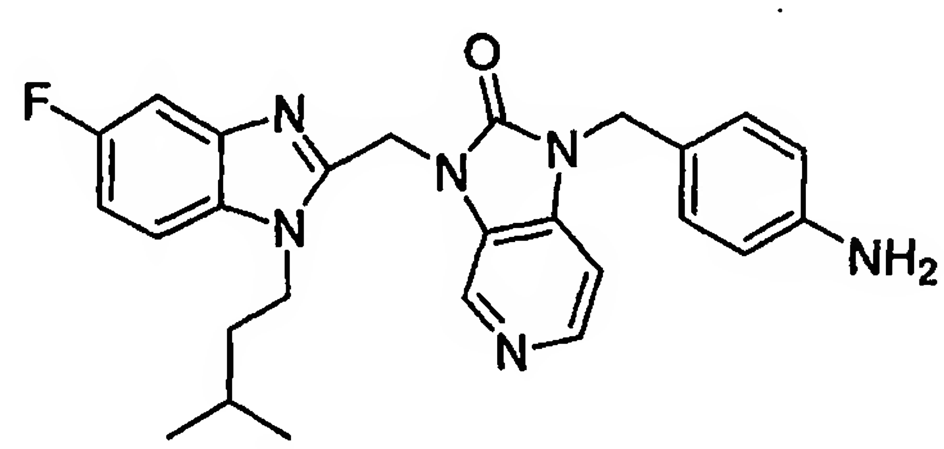
^{1}H NMR ($CDCl_3$) δ 0.99 (d, J = 6.7 Hz, 6 H), 1.54-1.59 (m, 2 H), 1.69-1.73 (m, 1 H), 4.29 (t, J = 9.2 H, 2 H), 5.20 (s, 2 H), 5.43 (s, 2 H), 6.86 (d, J = 5.4 Hz, 1 H), 7.05 (dt, J = 2.4, 9.1 Hz, 1 H), 7.24 (dd, J = 4.5, 8.9 Hz, 1 H), 7.41 (dd, J = 2.4, 9.3 Hz, 1 H), 7.49 (d, J = 8.7 Hz, 2 H), 8.21 (d, J = 8.7 Hz, 2 H), 8.29 (d, J = 5.2 Hz, 1 H), 8.76 (s, 1 H);

IR (KBr, cm^{-1}) 3424, 2959, 1716, 1611, 1524, 1492, 1346, 1176, 1137, 800;

MS m/e 489 (MH^+).

Anal. Calcd for $C_{26}H_{25}FN_3O_3$:		C, 63.92; H, 5.16; N, 17.20
	Found:	C, 63.95; H, 5.13; N, 17.22.

Example 19



A mixture of Example **18** (1.52 g, 3.11 mmol) and 10% palladium on carbon (150 mg) in MeOH (50 mL) and concentrated hydrochloric acid (1 mL) was aggitated under hydrogen at 55 psi for 1.5 hours. The reaction mixture was filtered through a pad of Celite, rinsing thoroughly with MeOH. The filtrate was evaporated and dried under vacuum to give Example **19** as an HCl salt (1.82 g, quantitative yield).

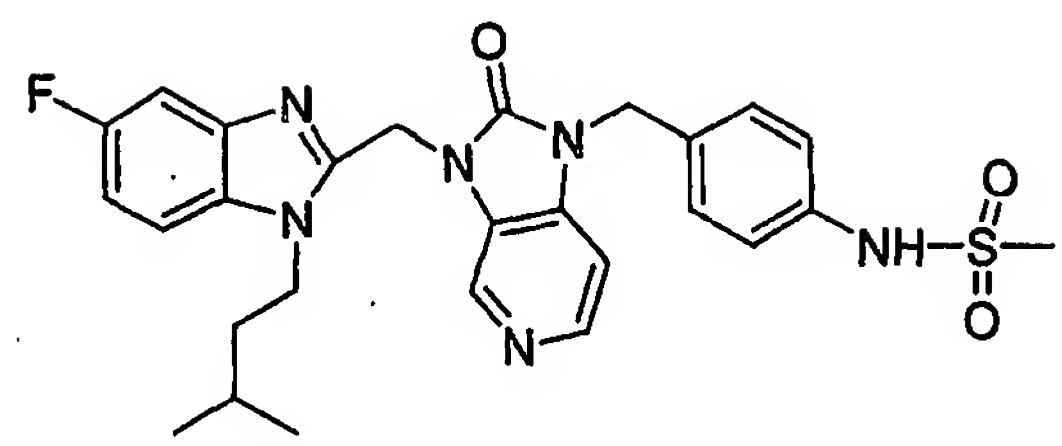
^{1}H NMR (CD_3OD) δ 1.09 (d, J = 6.0 Hz, 6 H), 1.84-1.90 (m, 3 H), 4.64 (t, J = 7.6 Hz, 2 H), 5.40 (s, 2 H), 5.94 (s, 2 H), 7.43-7.47 (m, 3 H), 7.52 (dd, J = 2.3, 8.1 Hz, 1 H), 7.70 (d, J = 8.3 Hz, 2 H), 7.87 (d, J = 6.5 Hz, 1 H), 7.93 (dd, J = 4.2, 9.1 Hz, 1 H), 8.59 (d, J = 6.4 Hz, 1 H), 9.01 (s, 1 H);

IR (KBr, cm^{-1}) 3411, 2869, 1748, 1655, 1621, 1517, 1496, 1130, 810;

MS m/e 459 (MH^+);

Anal. Calcd for $C_{26}H_{27}FN_6O_3 \bullet 3HCl \bullet 2.5H_2O$:		C, 50.95; H, 5.76; N, 13.71
	Found:	C, 50.72; H, 5.47; N, 13.66.

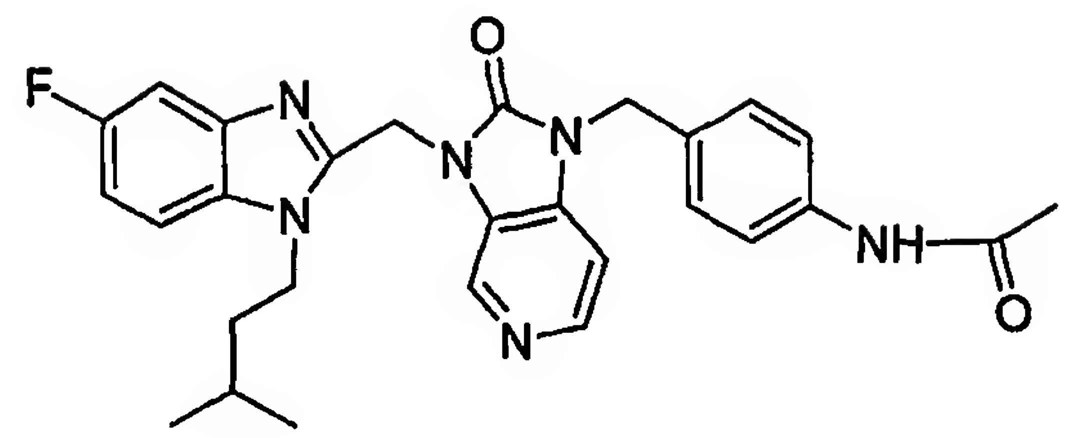
Example 20



To a mixture of Example **19** (350 mg, 0.66 mmol) and triethylamine (200 mg, 1.98 mmol) in CH_2Cl_2 cooled to 0 °C was added methanesulfonyl chloride (75 mg, 0.66 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for 16 hours. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL) and brine solution (10 mL). The aqueous layer was back-extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, and evaporated. Trituration of the resulting pale yellow solid with Et_2O gave the title compound (quantitative yield).

^{1}H NMR (CD_3OD) δ 1.06 (d, J = 6.3 Hz, 6 H), 1.75-1.81 (m, 3 H), 2.93 (s, 3 H), 4.46 (t, J = 8.2 Hz, 2 H), 5.28 (s, 2 H), 5.64 (s, 2 H), 7.18 (t, J = 2.5, 9.2 Hz, 1 H), 7.23-7.29 (m, 3 H), 7.46 (d, J = 8.6 Hz, 2 H), 7.60 (dd, J = 4.4, 8.9 Hz, 1 H), 7.77 (d, J = 6.5 Hz, 1 H), 8.48 (d, J = 6.7 Hz, 1 H), 8.78 (s, 1 H);
IR (KBr, cm^{-1}) 3441, 2959, 1736, 1617, 1515, 1332, 1150, 1040, 821;
MS m/e 537 (MH^+);
Anal. Calcd for $C_{27}H_{29}FN_6O_3S \bullet 4.5H_2O$: C, 52.50; H, 6.20; N, 13.61
Found: C, 52.20; H, 5.79; N, 12.79.

Example 21



To a mixture of Example **19** (400 mg, 0.75 mmol) and triethylamine (229 mg, 2.26 mmol) in CH_2Cl_2 cooled to 0 °C was added acetyl chloride (74 mg, 0.94 mmol) followed by a catalytic amount of dimethylaminopyridine (10 mg). The reaction was allowed to warm to room temperature and a pale yellow precipitate came out of solution. After 1 hour, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate solution and brine. The aqueous layer was back-extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, and evaporated. Trituration of the resulting white solid with Et_2O gave Example **21** (321 mg, 85% yield).

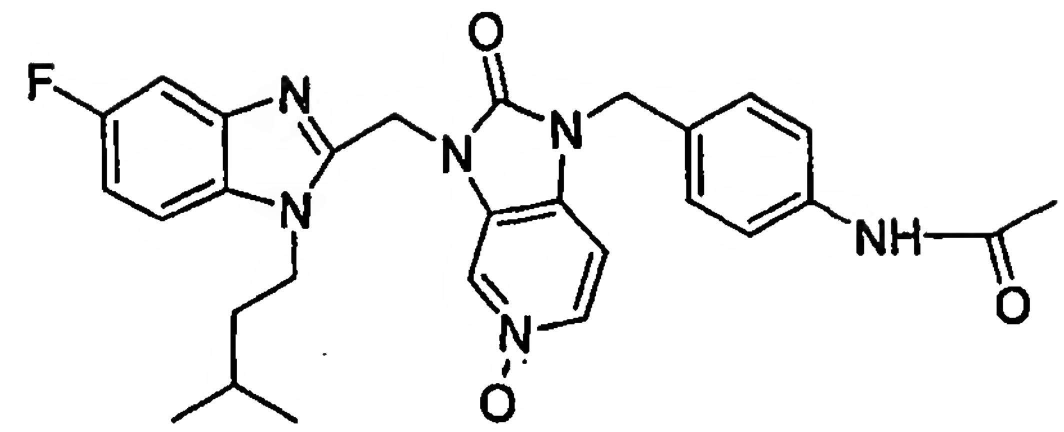
^{1}H NMR (CD_3OD) δ 0.96 (d, J = 0.96 Hz, 6 H), 1.54-1.59 (m, 2 H), 1.67-1.70 (m, 1 H), 2.10 (s, 3 H), 4.36 (t, J = 8.2 Hz, 2 H), 5.13 (s, 2 H), 5.51 (s, 2 H), 7.11 (dt, J = 2.5, 9.2 Hz, 1 H), 7.21 (d, J = 5.4 Hz, 1 H), 7.30 (dd, J = 2.4,9.3 Hz, 1 H), 7.37 (d, J =8.6 Hz, 2 H), 7.49 (dd, J = 4.5, 9.0 Hz, 1 H), 7.54 (d, J = 8.6 Hz, 2 H), 8.19 (d, J = 5.4 Hz, 1 H), 8.35 (s, 1 H);

IR (KBr, cm^{-1}) 3424, 2960, 1724, 1691, 1610, 1517, 1507, 1455, 1402, 1319, 1136, 810;

MS m/e 501 (MH^+);

Anal. Calcd for $C_{28}H_{29}FN_6O_2 \bullet 0.5H_2O$:	C, 66.00; H, 5.93; N, 16.49
Found:	C, 65.79; H, 6.12; N, 16.29.

Example 22

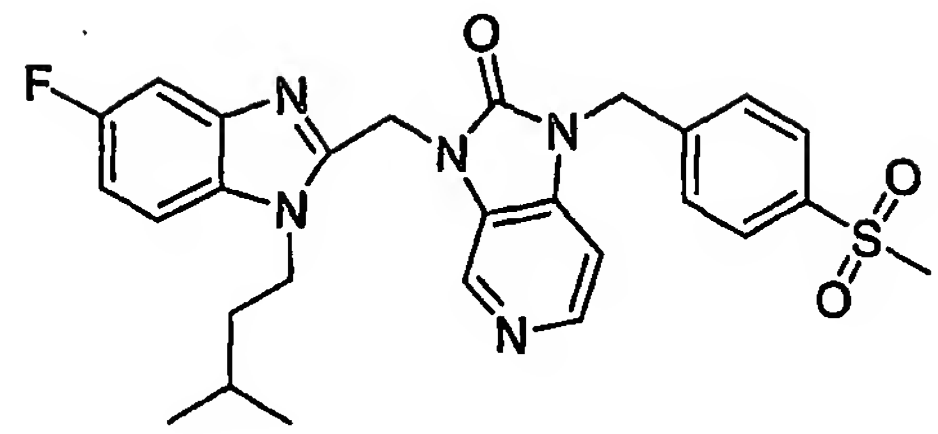


To a solution of the Example **20** (50 mg, 0.10 mmol) in DMF (5 mL) was added *m*-chloroperbenzoic acid (34 mg, 0.20 mmol). The mixture was stirred at room temperature for 16 hours. The solvent was evaporated under reduced pressure. The resulting residue was triturated with water and filtered. The aqueous filtrate was extracted with EtOAc and the combined extracts were dried over $MgSO_4$, and evaporated. The residue combined with the solid obtained from trituration were subjected to flash chromatography (gradient, CH_2Cl_2/5% ammonium hydroxide in MeOH, 40:1 to 20:1) to give Example **22** as a white solid (21 mg, 41% yield).

^{1}H NMR (DMSO-d_6) δ 0.95 (d, J = 6.5 Hz, 6 H), 1.57-1.60 (m, 2 H), 1.66-1.74 (m, 1 H), 2.02 (s, 3 H), 4.32 (t, J = 7.7 Hz, 2 H), 5.05 (s, 2 H), 5.41 (s, 2 H), 7.13 (t, J = 8.7 Hz, 1 H), 7.24 (d, J = 6.7 Hz, 1 H), 7.29 (d, J = 8.2 Hz, 1 H), 7.41 (d, J = 8.6 Hz, 1 H), 7.54 (d, J = 8.2 Hz, 1 H), 7.55-7.59 (m, 1 H), 7.96 (d, J = 6.3 Hz, 1 H), 8.37 (s, 1 H);
IR (KBr, cm^{-1}) 3428, 2956, 1720, 1678, 1600, 1551, 1514, 1465, 1407, 1320, 1162, 1146, 802;
MS m/e 517 (MH^+);

Anal. Calcd for $C_{28}H_{29}FN_6O_3 \bullet 0.5H_2O$:		C, 63.99; H, 5.75; N, 15.99
	Found:	C, 64.08; H, 5.57; N, 15.82.

Example 23

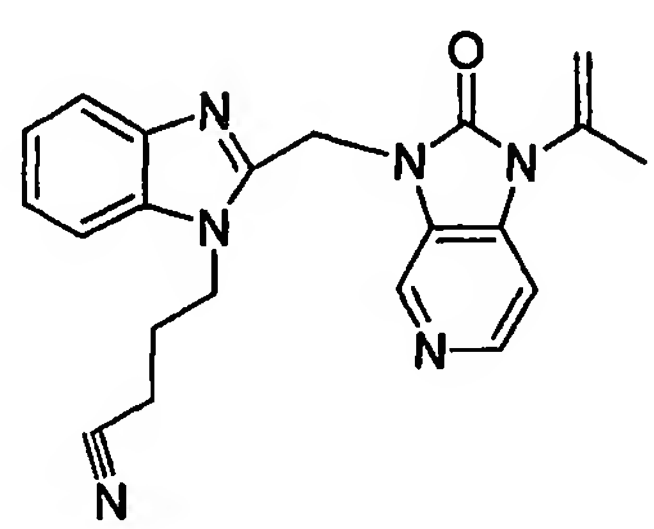


^{1}H NMR (CD_3OD) δ 0.98 (d, J = 6.6 Hz, 6 H), 1.59-1.64 (m, 2 H), 1.69-1.73 (m, 1 H), 3.09 (s, 3 H), 4.39 (t, J = 8.1 Hz, 2 H), 5.31 (s, 2 H), 5.52 (s, 2 H), 7.12 (dt, J = 2.5, 9.2 Hz, 1 H), 7.23 (d, J = 5.4 Hz, 1 H), 7.29 (dd, J = 2.4, 9.2 Hz, 1 H), 7.51 (dd, J = 4.5, 8.9 hz, 1 H), 7.66 (d, J = 8.4 Hz, 2 H), 7.94 (d, J = 8.4 Hz, 2 H), 8.22 (d, J = 1.7 Hz, 1 H), 8.39 (s, 1 H);

IR (KBr, cm^{-1}) 3423, 2959, 1715, 1613, 1602, 1497, 1454, 1407, 1307, 1148, 1090, 808, 520;

MS m/e 522 (MH^+).

Example 24



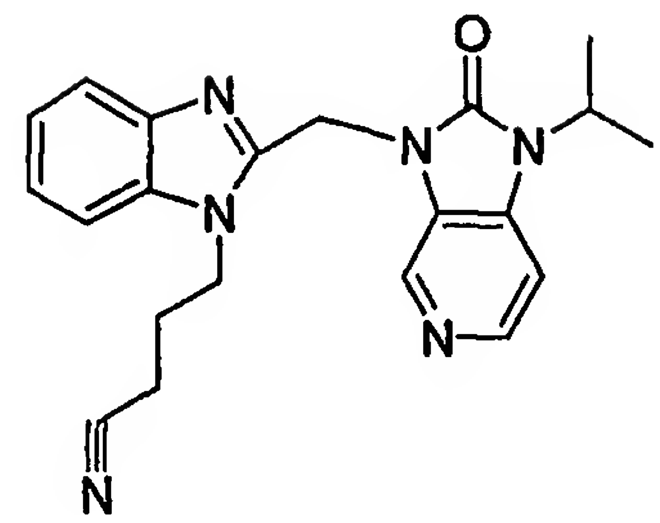
^{1}H NMR (CD_3OD) δ 1.85-1.90 (m, 2 H), 1.90 (s, 3 H), 2.27 (t, J = 7.5 Hz, 2 H), 4.29-4.34 (t, J = 7.5 Hz, 2 H), 5.03 (s, 1 H), 5.65 (s, 1 H), 6.86 (d, J = 5.5 Hz, 1 H), 7.12-7.22 (m, 3 H), 7.60-7.63 (m, 1 H), 8.16 (d, J = 5.5 Hz, 1 H), 8.65 (s, 1 H);

IR (KBr, cm^{-1}) 3396, 2244, 1710, 1660, 1604, 1493, 1458, 1399, 1332, 1166, 1140, 824, 742;

MS m/e 373 (MH^+);

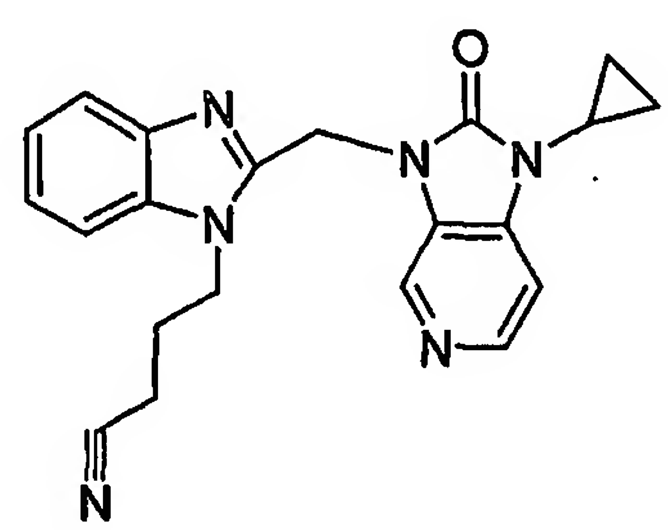
Anal. Calcd for $C_{22}H_{25}N_5O \bullet 0.25\ H_2O$:	C, 66.92; H, 5.48; N, 22.30
Found:	C, 66.58; H, 5.56; N, 22.34.

Example 25



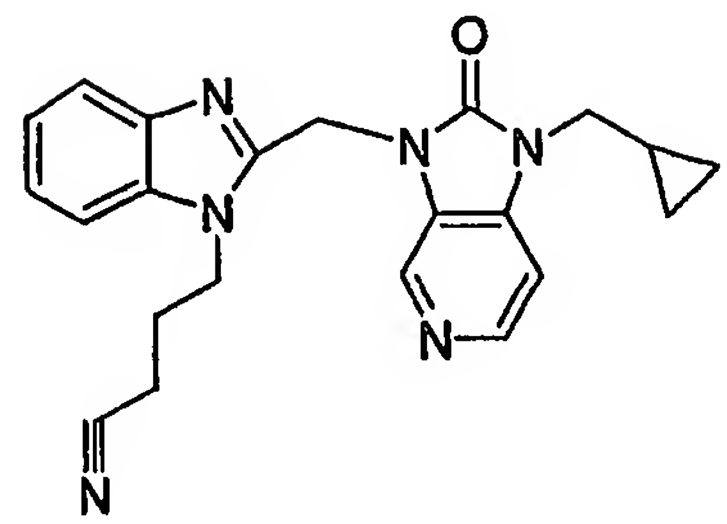
^{1}H NMR ($CDCl_3$) δ 1.56 (d, J = 6.9 Hz, 6 H), 1.98-2.08 (m, 2 H), 2.45 (t, J = 7.2 Hz, 2 H), 4.49 (t, J = 7.2 Hz, 2 H), 4.70-4.74 (m, 1 H), 5.40 (s, 2 H), 7.06 (d, J = 5.2 Hz, 1 H), 7.33-7.39 (m, 3 H), 7.78-7.81 (m, 1 H), 8.31 (d, J = 5.2 Hz, 1 H), 8.81 (s, 1 H);
IR (KBr, cm^{-1}) 3412, 2981, 2246, 1700, 1608, 1496, 1459, 1391, 1117, 748;
MS m/e 375 (MH^+).

Example 26



^{1}H NMR ($CDCl_3$) δ 1.03-1.06 (m, 2 H), 1.97-1.24 (m, 2 H), 2.13-2.18 (m, 2 H), 2.47 (t, J = 4.2 Hz, 2 H), 2.96-3.00 (m, 1 H), 4.51 (t, J = 4.4 Hz, 2 H), 4.16 (s, 2 H), 7.27-7.35 (m, 4 H), 7.38 (dd, J = 0.8, 4.2 Hz, 1 H), 7.77 (dd, J = 0.9, 4.4 Hz, 1 H), 8.37 (d, J = 3.4 Hz, 1 H), 8.56 (s, 1 H);
IR (KBr, cm^{-1}) 3405, 2245, 1702, 1608, 1500, 1408, 1172, 1024, 820, 743;
MS m/e 373 (MH^+);
Anal. Calcd for $C_{21}H_{20}N_8O{\bullet}0.875H_2O$: C, 64.98; H, 5.64; N, 21.65
Found: C, 65.06; H, 5.36; N, 21.51.

Example 27

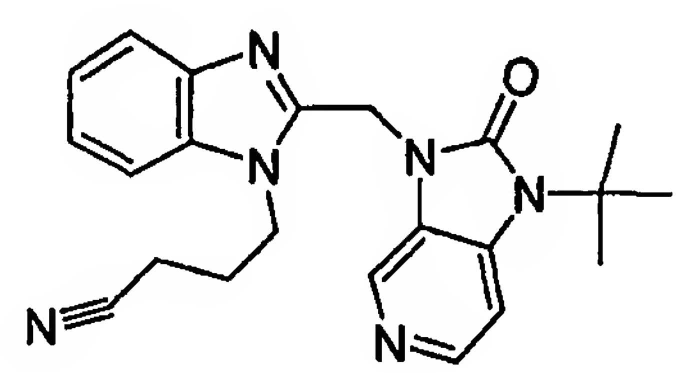


^{1}H NMR (CD_3OD) δ 0.53-0.54 (m, 2 H), 0.64-0.66 (m, 2 H), 1.31-1.37 (m, 1 H), 2.30-2.34 (m, 2 H), 2.68 (t, J = 7.2 Hz, 2 H), 4.02 (d, J = 7.2 Hz, 2 H), 4.63 (t, J = 7.4 Hz, 2 H), 5.72 (s, 2 H), 7.39 (t, J = 7.0 Hz, 1 H), 7.43 (t, J = 7.1 Hz, 1 H), 7.63 (d, J = 7.9 Hz, 1 H), 7.73 (d, J = 8.1 Hz, 2 H), 7.92 (d, J = 6.5 Hz, 1 H), 8.55 (d, J = 6.5 Hz, 1 H), 8.81 (s, 1 H);

IR (KBr, cm^{-1}) 3448, 2250, 1748, 1676, 1522, 1201, 1131, 720;

MS m/e 387 (MH^+).

Example 28

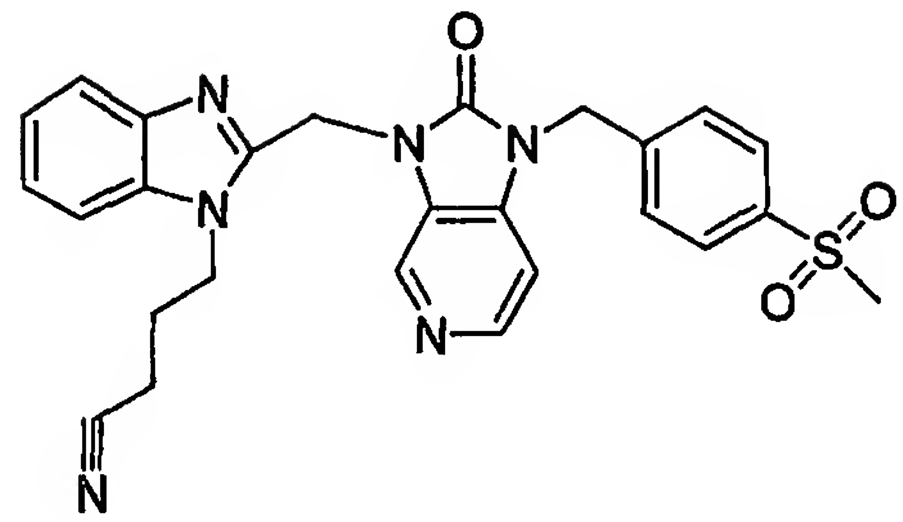


^{1}H NMR ($CDCl_3$) δ 1.81 (s, 9 H), 2.05-2.06 (m, 2 H), 2.46 (t, J = 7.2 Hz, 2 H), 4.48 (t, J = 7.6 Hz, 2 H), 5.38 (s, 2 H), 7.31-7.36 (m, 4 H), 7.78 (m, 1 H), 8.24 (d, J = 5.8 Hz, 1 H), 8.84 (s, 1 H);

IR (KBr, cm^{-1}) 3406, 2937, 2246, 1706, 1493, 1458, 1387, 1157, 1138, 746;

MS m/e 389 (MH^+).

Example 29



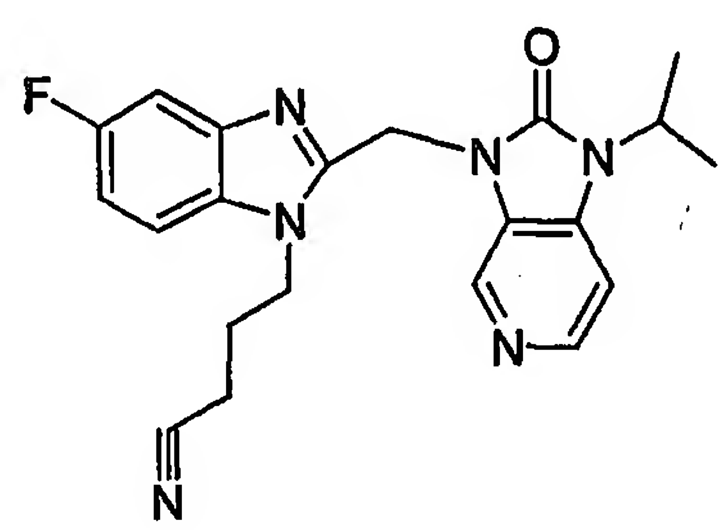
^{1}H NMR (DMSO-d_6) δ 2.09-2.12(m, 2 H), 2.63 (t, J = 7.4 Hz, 2 H), 4.43 (t, J = 7.5 Hz, 2 H), 5.28 (s, 2 H), 5.52 (s, 2 H), 7.21 (t, J = 7.2 Hz, 1 H), 7.26 (t, J = 7.2 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.60-7.63 (m, 4 H), 7.92 (d, J = 8.4 Hz, 2 H), 8.23 (d, J = 5.3 Hz, 1 H), 8.50 (s, 1 H);

IR (KBr, cm^{-1}) 3426, 2246, 1716, 1407, 1150, 760;

MS m/e 501 (MH$^+$);

Anal. Calcd for $C_{27}H_{28}FN_5O_3S$:	C, 62.17; H, 5.17; N, 13.43
Found:	C, 62.03; H, 5.45; N, 13.34.

Example 30



^{1}H NMR (CDCl$_3$) δ 1.54 (d, J = 7.0 Hz, 6 H), 1.99-2.05 (m, 2 H), 2.45 (t, J = 7.2 Hz, 2 H), 4.47 (t, J = 7.6 Hz, 2 H), 4.70 (m, 1H), 5.36 (s, 2 H), 7.06-7.10 (m, 2 H), 7.27-7.30 (m, 1 H), 7.45 (q, J =2.4, 9.1 Hz, 1 H), 8.31 (d, J = 4.0 Hz, 1 H), 8.78 (s, 1 H);

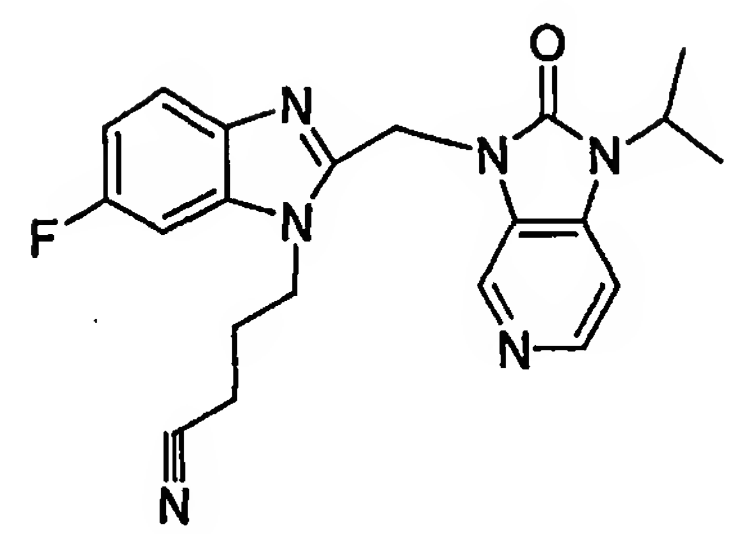
IR (KBr, cm^{-1}) 3432, 2953, 2360, 2245, 1718, 1698, 1284, 1139;

MS m/e 393 (MH$^+$);

Anal. Calcd for $C_{21}H_{21}FN_6O$: C, 64.27; H, 5.39; N, 21.41

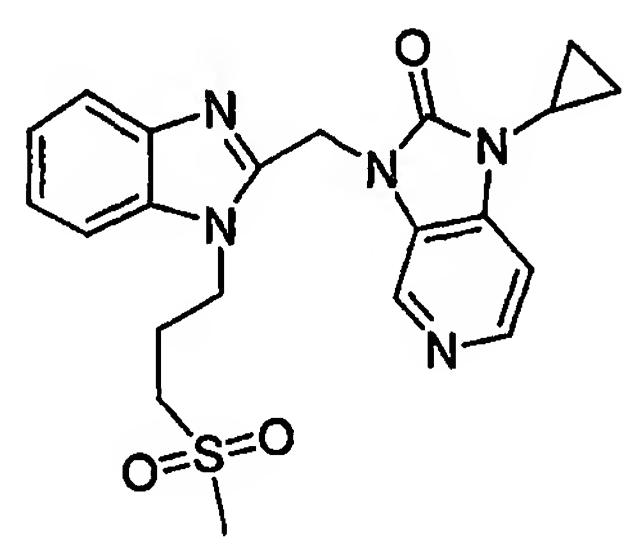
Found: C, 64.23, H, 5.44; N, 21.24.

Example 31



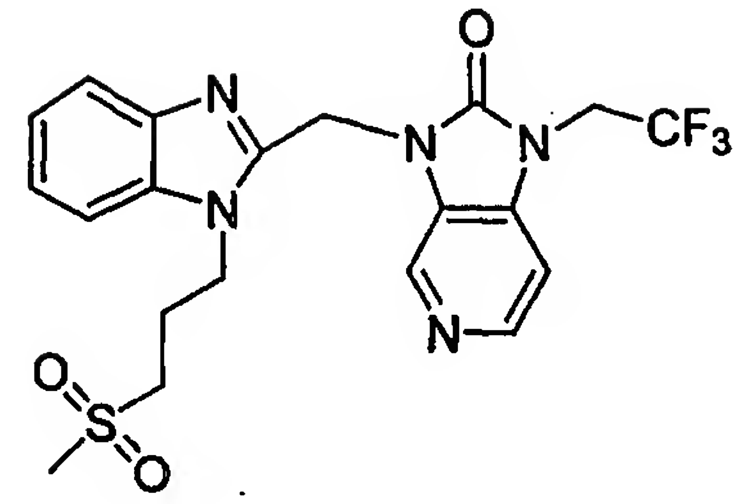
^{1}H NMR ($CDCl_3$) δ 1.53 (d, J = 7.0 Hz, 6 H), 1.96-2.03 (m, 2 H), 2.45 (t, J = 7.2 Hz, 2 H), 4.41 (t, J = 7.6 Hz, 2 H), 4.70 (m, 1 H), 5.34 (s, 2 H), 6.99-7.06 (m, 3 H), 7.67-7.70 (m, 1 H), 8.29 (d, J = 4.0 Hz, 1H), 8.76 (s, 1 H);
IR (KBr, cm^{-1}) 3423, 2941, 2247, 1710, 1492, 1390, 808;
MS m/e 393 (MH^+).

Example 32



^{1}H NMR ($CDCl_3$) δ 1.03-1.06 (m, 2 1.17-1.22 (m, 2H), 2.25-2.31 (m, 2 H), 2.93 (s, 3 H), 2.98-3.01 (m, 1 H), 3.10 (t, J = 7.4 Hz, 2 H), 4.54 (t, J = 7.5 Hz, 2 H), 5.42 (s, 2 H), 7.25-7.39 (m, 4 H), 7.76 (d, J = 7.1 Hz, 1 H), 8.36 (d, J = 5.3 Hz, 1 H), 8.79 (s, 1 H);
IR (KBr, cm^{-1}) 3423, 2927, 1718, 1608, 1499, 1459, 1409, 1311, 1289, 1128, 748;
MS m/e 426(MH^+);
Anal. Calcd for $C_{21}H_{23}N_5O_3S$: C, 59.27; H, 5.44; N, 16.45
Found: C, 59.03; H, 5.52; N, 16.31.

Example 33



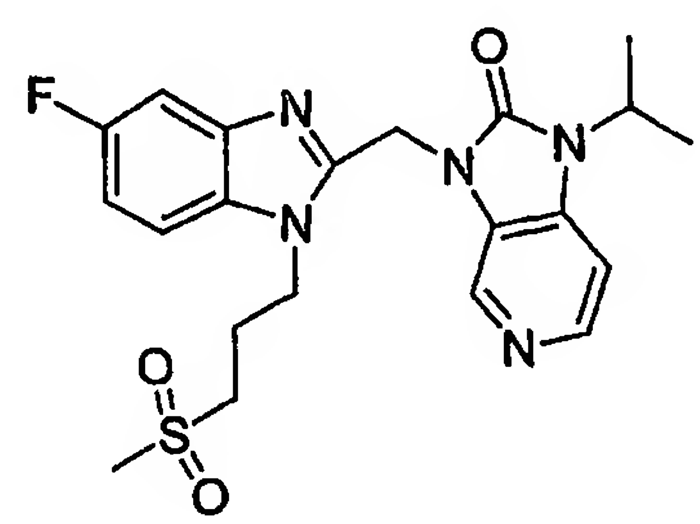
^{1}H NMR (DMSO-d_6) δ 2.13-2.20 (m, 2 H), 3.01 (s, 3 H), 3.26 (t, J = 7.8 Hz, 2 H), 4.50 (t, J = 7.5 Hz, 2 H), 4.91 (q, J = 9.3 Hz, 2 H), 5.53 (s, 2 H), 7.20 (t, J = 7.3 Hz, 1 H), 7.28 (t, J = 7.7 Hz, 1 H), 7.45 (d, J = 5.3 Hz, 1 H), 7.64 (d, J = 8.1 Hz, 1 H) 8.32 (d, J = 5.3 Hz, 1 H), 8.52 (s, 1 H);

IR (KBr, cm^{-1}) 3441, 1725, 1498, 1460, 1408, 1294, 1265, 1167, 1125, 746;

MS m/e 468 (MH$^+$);

Anal. Calcd for $C_{20}H_{20}F_3N_5O_3S$•0.375 H_2O:	C, 50.66; H, 4.41; N, 14.76
Found:	C, 50.83; H, 4.34; N, 14.41.

Example 34



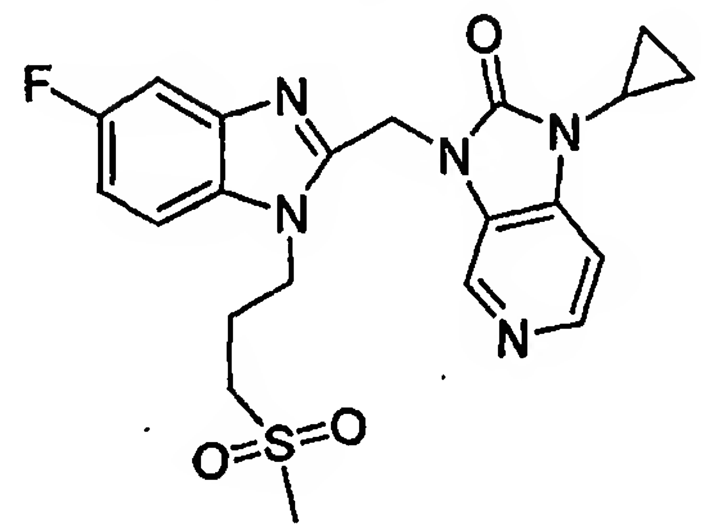
^{1}H NMR (CD_3OD) δ 1.47 (d, J = 6.9 Hz, 6 H), 2.14-2.17 (m, 2 H), 3.00 (s, 3 H), 3.24 (t, J = 7.8 Hz, 2 H), 4.50 (d, J = 7.5 Hz, 2 H), 4.63-4.66 (m, 1 H), 5.44 (s, 2 H), 7.16 (dt, J = 2.5, 9.2 Hz, 1 H), 7.41-7.45 (m, 2 H), 7.67 (dd, J = 4.8, 8.9 Hz, 1 H), 8.23 (d, J = 5.4 Hz, 1 H), 8.47 (s, 1 H);

IR (KBr, cm^{-1}) 3423, 2984, 2937, 1702, 1608, 1495, 1457, 1391, 1293, 1135, 1116, 963, 809;

MS m/e 446 (MH$^+$);

Anal. Calcd for $C_{21}H_{24}FN_5O_3S$: C, 56.61; H, 5.43; N, 15.71
Found: C, 56.46; H, 5.55; N, 15.62.

Example 35

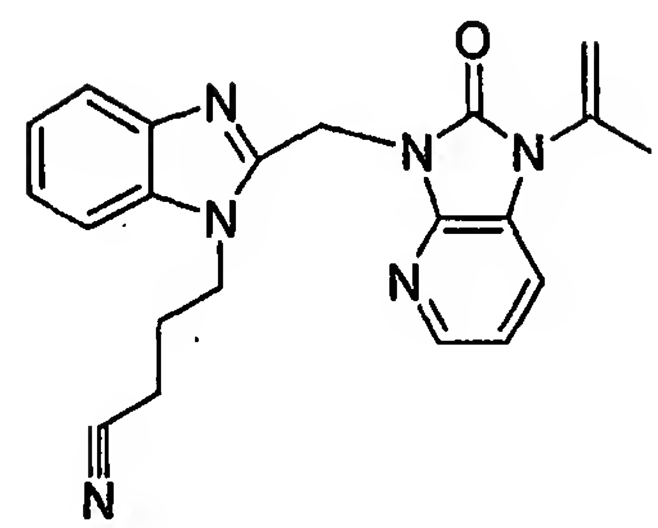


^{1}H NMR (CD_3OD) δ 0.91-0.93 (m, 2 H), 1.06-1.07 (m, 2 H), 2.99-3.01 (m, 1 H), 3.00 (s, 3 H), 3.23 (t, J = 7.7 Hz, 2 H), 4.49 (t, J = 7.5 Hz, 2 H), 5.41 (s, J = 2 H), 7.15 (dt, J = , 1 H), 7.29 (dd, J = 2.0, 5.3 Hz, 1 H), 7.43 (dd, J = 2.5, 9.8 Hz, 1 H), 7.67 (dd, J = 4.7, 8.9 Hz, 1 H), 8.26 (d, J = 5.3 Hz, 1 H), 8.44 (s, 1 H);
IR (KBr, cm^{-1}) 3423, 3014, 1708, 1609, 1498, 1455, 1415, 1315, 1294, 1171, 1131, 957, 819;
MS m/e 444 (MH^+);
Anal. Calcd for $C_{21}H_{22}FN_5O_3S$: C, 56.87; H, 5.00; N, 15.79
Found: C, 56.76; H, 5.15; N, 15.69.

Example **35** was converted to an oxalate salt by adding 1 equivalent of oxalic acid to a MeOH solution of **35** and evaporating the solvent.

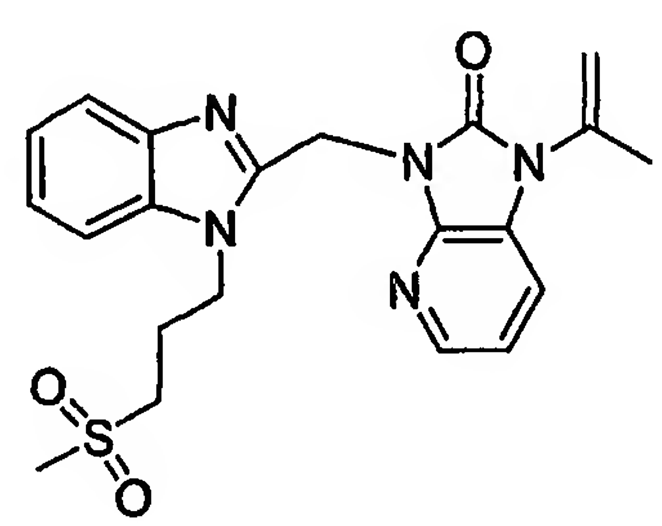
^{1}H NMR (CD_3OD) δ 2.26 (s, 3 H), 2.26-2.36 (m, 2 H), 2.64 (t, J = 7.5 Hz, 2 H), 4.62 (t, J = 7.5 Hz, 2 H), 5.29 (s, 1 H), 5.45 (s, 1 H), 5.58 (s, 2 H), 7.16 (dd, J = 5.4, 8.1 Hz, 1 H), 7.34-7.44 (m, 2 H), 7.54-7.71 (m, 2 H), 7.70 (d, J = 8.1 Hz, 1 H), 8.01 (dd, J = 0.9, 5.4 Hz, 1 H);
IR (KBr, cm^{-1}) 3405, 2954, 2244, 1702, 1611, 1476, 1456, 1400, 1276, 1188, 1158, 795, 749;
MS m/e 373 (MH^+);
Anal. Calcd for $C_{21}H_{20}N_6O{\bullet}C_2H_2O_4{\bullet}0.25H_2O$: C, 59.16; H, 4.86; N, 18.00
Found: C, 58.90; H, 4.83; N, 18.24.

Example 36



^{1}H NMR ($CDCl_3$) δ 2.19-2.45 (m, 2 H), 2.45 (s, 3 H), 2.48 (t, J = 7.1 Hz, 2 H), 4.61 (t, J = 7.4 Hz, 2 H), 5.19 (s, 1 H), 5.34 (s, 1H), 5.48 (s, 2 H), 7.03 (dd, J = 5.2, 7.9 Hz, 1 H), 7.26-7.33 (m, 3 H), 7.80 (d, J = 8.0 Hz, 1 H), 8.10 (dd, J = 1.4, 5.2 Hz, 1 H).

Example 37



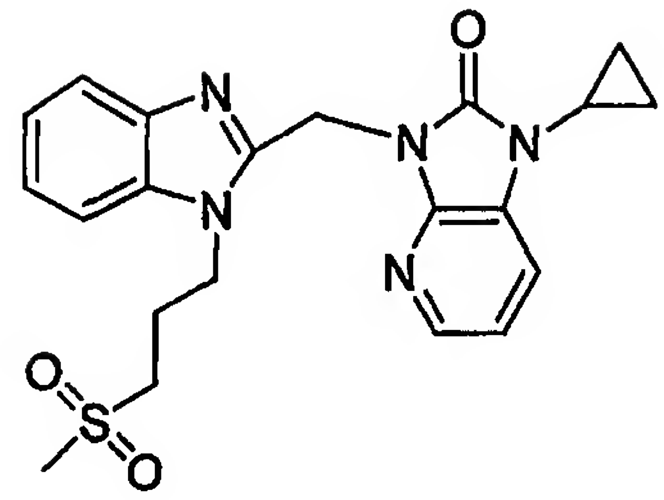
^{1}H NMR ($CDCl_3$) δ 2.28-2.34 (s over m, 5 H), 2.94 (s, 3 H), 3.16 (t, J = 7.2 Hz, 2 H), 4.59 (t, J = 7.9 Hz, 2 H), 5.37 (s, 1 H), 5.47 (s, 1 H), 5.54 (s, 2 H), 7.08 (dd, J = 5.3, 7.8 Hz, 1 H), 7.39-7.43 (m, 2 H), 7.51 (d, J = 7.7 Hz, 1 H), 7.85 (d, J = 7.3 Hz, 1 H), 8.05 (bs, 1 H), 8.09 (dd, J = 1.0, 5.2 Hz, 1 H);

IR (KBr, cm^{-1}) 3423, 1708, 1618, 1453, 1402, 1295, 1131, 750;

MS m/e 426 (MH^+);

Anal. Calcd for $C_{21}H_{23}N_5O_3S$:	C, 59.28; H, 5.44; N, 16.45
Found:	C, 59.11; H, 5.36; N, 16.35.

Example 38

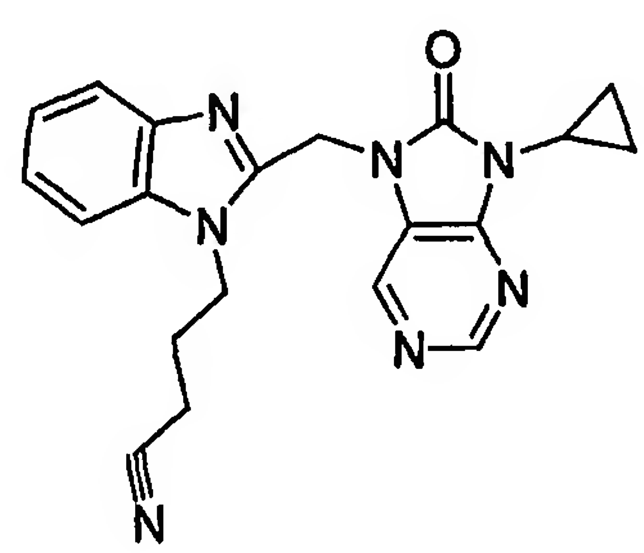


^{1}H NMR ($CDCl_3$) δ 1.06-1.11 (m, 4 H), 2.49-2.54 (m, 2 H), 2.94-2.99 (m, 1 H), 3.24 (t, J = 6.7 Hz, 2 H), 4.75 (t, J = 7.1 Hz, 2 H), 5.70 (s, 2 H), 7.05 (dd, J = 5.3, 7.7 Hz, 1 H), 7.37-7.44 (m, 3 H), 7.54 (d, J = 8.0 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.98 (d, J = 4.8 Hz, 1 H);

IR (KBr, cm^{-1}) 3435, 1716, 1617, 1486, 1460, 1425, 1295, 1131, 747;

MS m/e 426 (MH^+).

Example 39



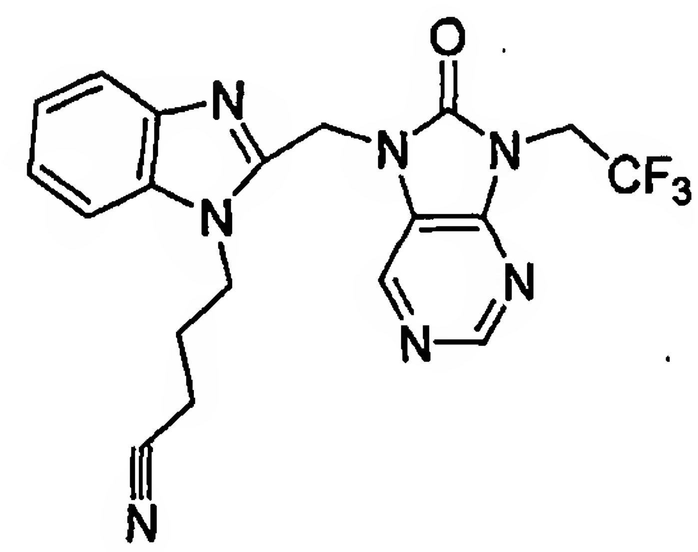
^{1}H NMR (DMSO-d_6) δ 1.02-1.07 (m, 4 H), 2.08-2.14 (m, 2 H), 2.64 (t, J = 7.4 Hz, 2 H), 3.02-3.03 (m, 1 H), 4.42 (t, J = 7.4 Hz, 2 H), 5.44 (s, 1 H), 7.19 (t, J = 7.5 Hz, 1 H), 7.28 (t, J = 7.2 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.0 Hz, 1 H), 8.46 (s, 1 H), 8.66 (s, 1 H);

IR (KBr, cm^{-1}) 3452, 2244,1731, 1718, 1612, 1488, 1422, 1407, 1317, 746;

MS m/e 374 (MH^+);

Anal. Calcd for $C_{20}H_{19}N_7O$:	C, 64.33; H, 5.12; N, 26.25
Found:	C, 64.00; H, 5.20; N, 26.12.

Example 40

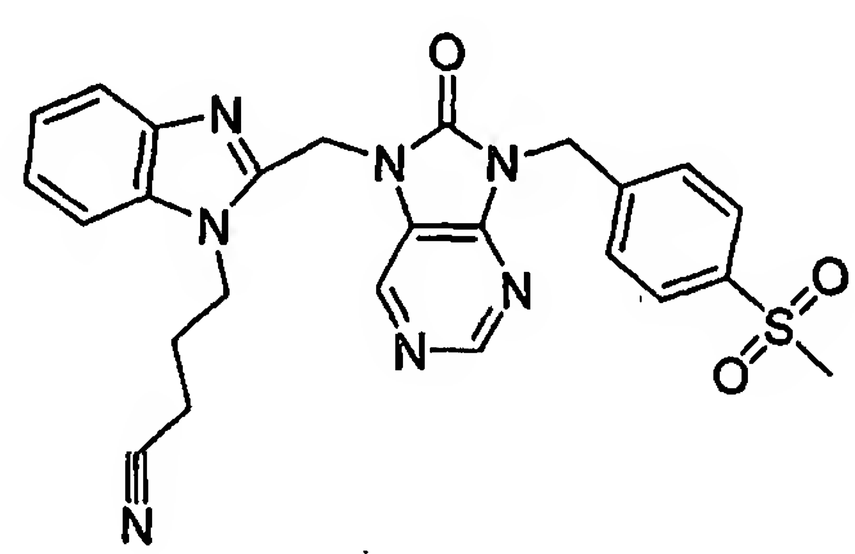


^{1}H NMR ($CDCl_3$) δ 2.07-2.13 (m, 2 H), 2.48 (t, J = 6.9 Hz, 2 H), 4.52 (d, J = 7.6 Hz, 2 H), 4.59-4.64 (m, 2 H), 5.47 (s, 2 H), 7.33-7.44 (m, 3 H), 7.80 (d, J = 7.5 Hz, 1 H), 8.76 (s, 1 H), 8.88 (s, 1 H);

MS m/e 416 (MH^+);

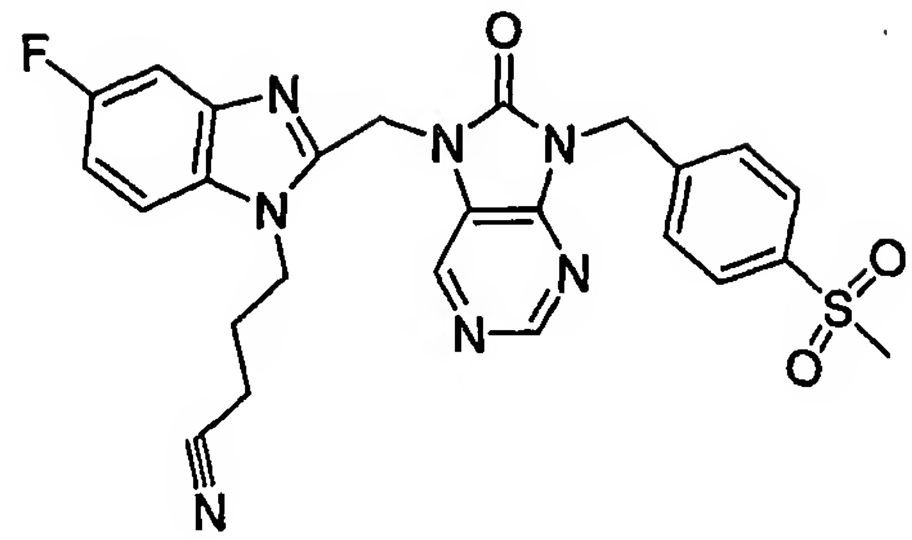
Anal. Calcd for $C_{19}H_{16}F_3N_7O$:	C, 54.94; H, 3.88; N, 23.60
Found:	C, 54.87; H, 3.78; N, 23.66.

Example 41



^{1}H NMR ($CDCl_3$) δ 2.12-2.15 (m, 2 H), 2.43 (t, J = 7.0 Hz, 2 H), 3.02 (s, 3 H), 4.51 (t, J = 7.4 Hz, 2 H), 5.22 (s, 2 H), 5.45 (s, 2 H), 7.32-7.42 (m, 3 H), 7.69 (d, J = 8.4 Hz, 2 H), 7.77-7.79 (m, 1 H), 7.91-7.93 (m, 2 H), 8.73 (s, 1 H), 8.83 (s, 1 H); MS m/e 502 (MH^+).

Example 42



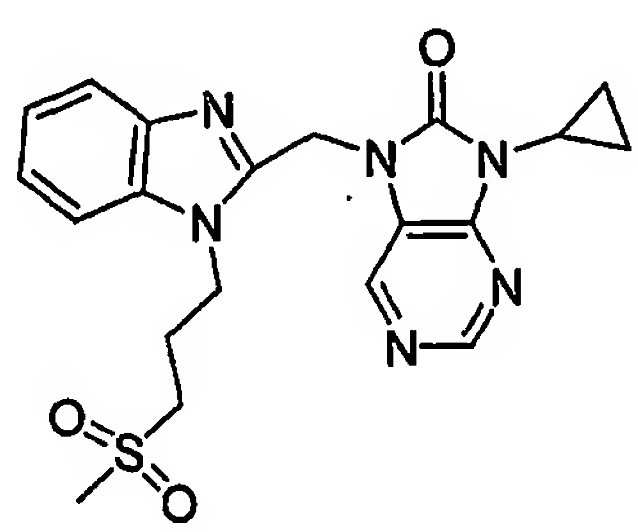
^{1}H NMR ($CDCl_3$) δ 2.12-2.15 (m, 2 H), 2.44 (t, J = 7.0 Hz, 2 H), 3.02 (s, 3 H), 4.49 (t, J = 7.4 Hz, 2 H), 5.23 (s, 2 H), 5.41 (s, 2 H), 7.10-7.14 (m, 1 H), 7.32-7.34 (m, 1 H), 7.43 (dd, J = 2.4, 9.0 Hz, 1 H), 7.69 (d, J = 8.3 Hz, 2H), 7.92 (d, J = 8.3 Hz, 2 H), 8.74 (s, 1 H), 8.80 (s, 1 H);

IR (KBr, cm^{-1}) 3441, 2928, 2244, 1718, 1609, 1492, 1406, 1300, 1150;

MS m/e 520 (MH^+);

Anal. Calcd. for $C_{25}H_{22}FN_3O_3S$:	C, 57.79; H, 4.26; N, 18.87
Found:	C, 57.49; H, 4.11; N, 18.55.

Example 43



^{1}H NMR ($CDCl_3$) δ 1.17-1.18 (m, 2 H), 2.31-2.37 (m, 2 H), 2.97 (s, 3 H), 3.01-3.06 (m, 1 H), 3.15 (t, J = 7.2 Hz, 2 H), 4.58 (t, J = 7.5 Hz, 2 H), 5.41 (s, 1 H), 7.30-7.36 (m, 2 H), 7.42 (d, J = 7.4 Hz, 1 H), 7.76-7.78 (dd, J = 1.2, 7.2 Hz, 1 H), 8.73(s, 1 H), 8.74 (s, 1 H);

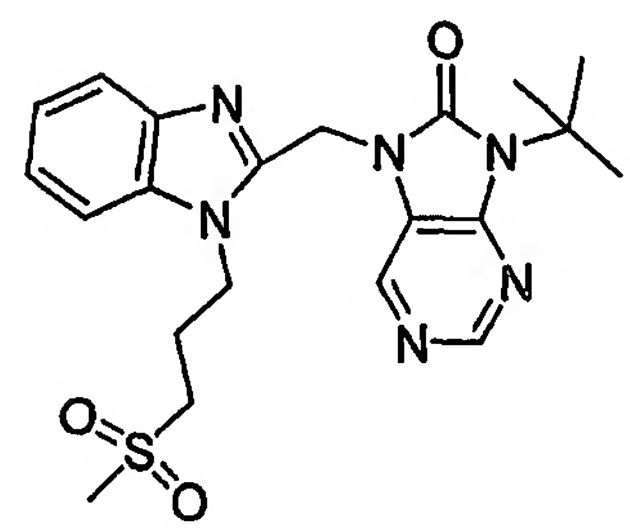
IR (KBr, cm^{-1}) 3424, 1721, 1615, 1493, 1407, 1313, 1126, 750;

MS m/e 427 (MH^+);

Anal. Calcd for $C_{20}H_{22}N_6OS \bullet H_2O$: C, 54.04; H, 5.44; N, 18.91

Found: C, 53.95; H, 5.54; N, 18.75.

Example 44

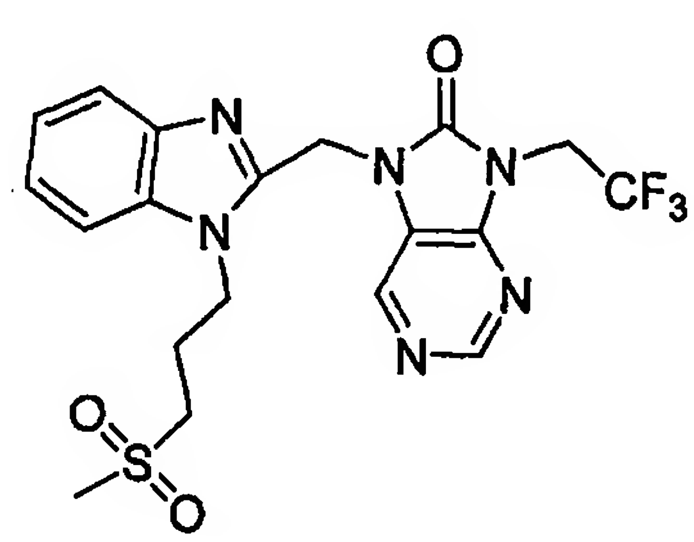


^{1}H NMR ($CDCl_3$) δ 1.84 (s, 9 H), 2.30-2.35 (m, 2 H), 3.13 (t, J = 7.2 Hz, 2H), 4.58 (t, J = 7.6 Hz, 2 H), 5.38 (s, 1 H), 7.30-7.35 (m, 2 H), 7.42 (d, J = 7.4 Hz, 1 H), 7.76-7.78 (dd, J = 1.2, 7.2 Hz, 1 H), 8.66 (s, 1 H), 8.73 (s, 1 H);
IR (KBr, cm^{-1}): 3431, 2927, 1718, 1616, 1469, 1444, 1469, 1444, 1296, 1134, 747;
MS m/e 443 (MH^+);

Anal. Calcd for $C_{21}H_{26}N_6O_3S\bullet H_2O$: C, 55.86; H, 6.03; N, 18.61

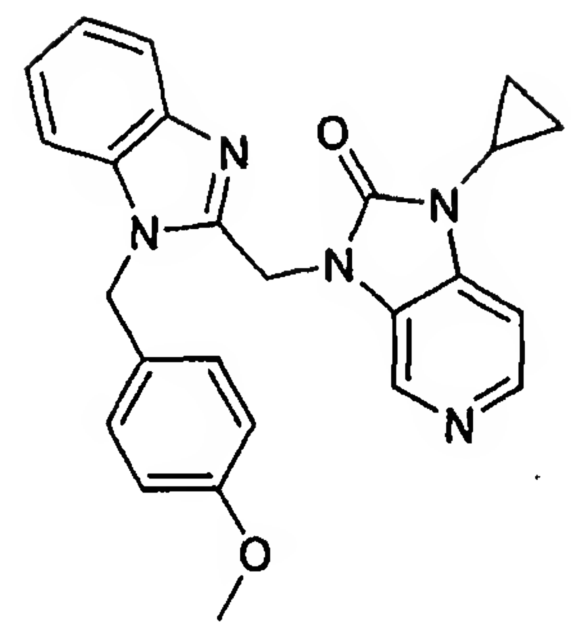
Found: C, 55.87; H, 5.88; N, 18.44.

Example 45



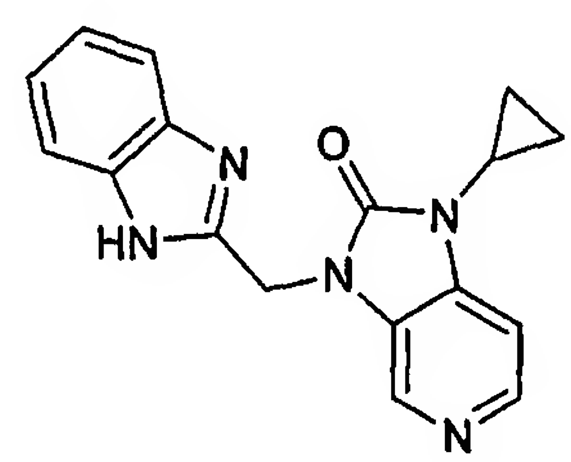
^{1}H NMR ($CDCl_3$) δ 2.25-2.29 (m, 2 H), 2.97 (s, 3 H), 3.14 (t, J = 7.0 Hz, 2 H), 4.56-4.64 (m, 4 H), 5.49 (s, 2 H), 7.32-7.39 (m, 2 H), 7.44 (d, J = 7.4 Hz, 1 H), 7.78-7.80 (dd, J = 1.4, 7.2 Hz, 1 H), 8.76 (s, 1 H), 8.85 (s, 1 H);
MS m/e 469 (MH^+).

Example 46



^{1}H NMR ($CDCl_3$) δ 0.71-0.74 (m, 2 H), 1.03-1.07 (m, 2 H), 2.63-2.66 (m, 1 H), 3.66 (s, 3 H), 5.39 (s, 2 H), 5.47 (s, 2 H), 6.50 (m, 4 H), 6.99 (d, J = 5.3 Hz, 1 H), 7.20 (d, J = 8.0 Hz, 1 H), 7.26 (m, 1 H), 7.31 (m, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 8.27 (d, J = 5.0 Hz, 1 H), 8.53 (s, 1 H);
MS m/e 426 (MH^+).

Example 47

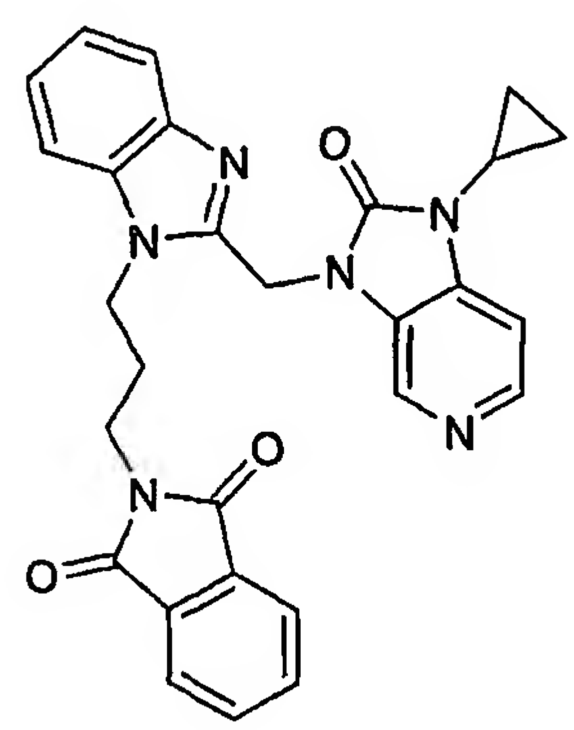


A stirred suspension of Example **46** (11.75 g, 27.6 mmol) in CH_3CN (150 mL) was treated with ceric ammonium nitrate (CAN, 60.60 g, 110 mmol) and diluted with water (25 mL) to give a homogeneous solution which was stirred at room temperature for 24 hours. The mixture was concentrated *in vacuo* to a volume of 50 mL, then diluted with H_2O (100 mL) and again concentrated until 100 mL remained and a yellow solid had precipitated from solution. The yellow solid was isolated from the chilled suspension by filtration and was identified as the 4-methoxybenzaldehyde by-product. The filtrate was then diluted with H_2O to 400 mL and MeOH (600 mL) was added. To the resulting solution was added a

saturated aqueous solution of sodium potassium tartrate until the pH of the solution reached 6 and a very finely divided powder precipitated. The reaction mixture was centrifuged and the liquid was decanted away from the solid and concentrated *in vacuo*. The residue was redissolved in water (250 mL) and the resulting solution was extracted with CH_2Cl_2 (8 x 100 mL). The organic extracts were combined and concentrated *in vacuo* to a brown glassy solid which was redissolved in minimum CH_2Cl_2. After a few minutes, a beige powder precipitated from solution. Et_2O was added to the mixture and the solid was isolated by filtration, rinsed with Et_2O, and dried under high vacuum to give 6.62 g (79 % yield) of Example **47** as a beige powder.

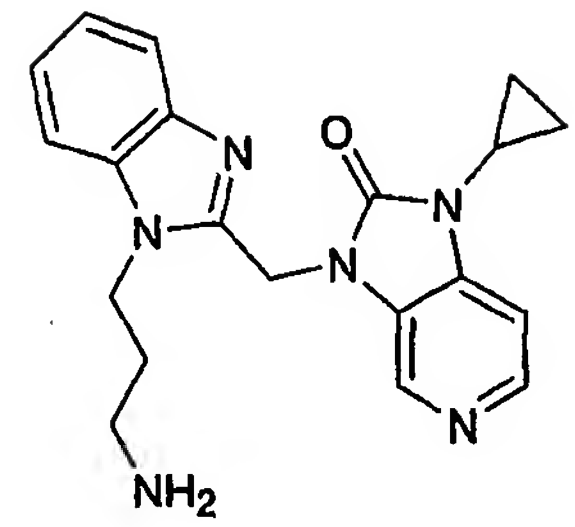
^1H NMR (DMSO-d_6) δ 0.92-0.97 (m, 2 H), 1.06-1.10 (m, 2 H), 2.97-3.01 (m, 1 H), 5.30 (s, 2 H), 7.14-7.17 (m, 2 H), 7.30 (d, J = 5.4 Hz, 1 H), 7.50 (bs, 2 H), 8.25-8.28 (m, 2 H), 12.54 (bs, 1 H);
MS m/e 306 (MH^+).

Example 48



^1H NMR ($CDCl_3$) δ 0.97-1.00 (m, 2 H), 1.12-1.16 (m, 2 H), 2.09-2.15 (m, 2 H), 2.99-3.03 (m, 1 H), 3.82 (t, J = 6.8 Hz, 2 H), 4.42 (t, J = 7.9 Hz, 2 H), 5.36 (s, 2 H), 7.21-7.28 (m, 3 H), 7.32 (d, J = 7.7 Hz, 1 H), 7.69-7.74 (m, 3 H), 7.81-7.85 (m, 2 H), 8.35 (d, J = 5.0 Hz, 1 H), 8.79 (s, 1 H);
MS m/e 493 (MH^+).

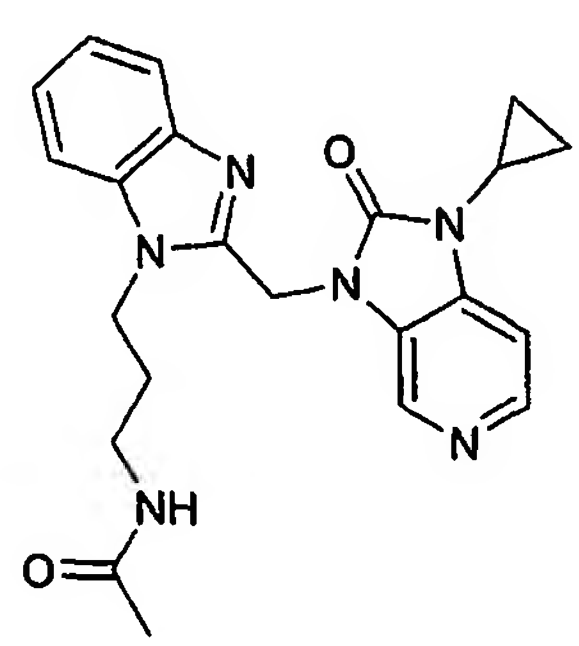
Example 49



Example **48** (2.58 g, 5.24 mmol) was treated with hydrazine hydrate (2.62 g, 52.4 mmol) in MeOH (100 mL) and the mixture was heated to reflux for 5 hours. The resulting mixture was passed through a 50 mL bed of AG 50W-X2 strong cation exchange resin (Bio-Rad Laboratories), and the bed was rinsed with MeOH (300 mL). The yellow eluent was discarded, and the product was eluted from the resin with 2M ammonia in MeOH (500 mL). The ammonia eluent was concentrated *in vacuo* to give 1.85 g (97 % yield) of Example **49** as an off-white powder.

^{1}H NMR (DMSO-d_6) δ 0.92 (s, 2 H), 1.07 (d, J = 5.8, 2 H), 1.74 (t, J = 6.8 Hz, 2 H), 2,57 (t, J = 6.2 Hz, 2 H), 2.99-3.01 (m, 1 H), 4.39 (t, J = 7.1 Hz, 2 H), 5.43 (s, 2 H), 7.17 (t, J = 7.4 Hz, 1 H), 7.24 (t, J = 7.5 Hz, 1 H), 7.29 (d, J = 5.1 Hz, 1 H), 7.58 (t, J = 8.6 Hz, 2 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.39 (s, 1 H);
MS m/e 363 (MH^+).

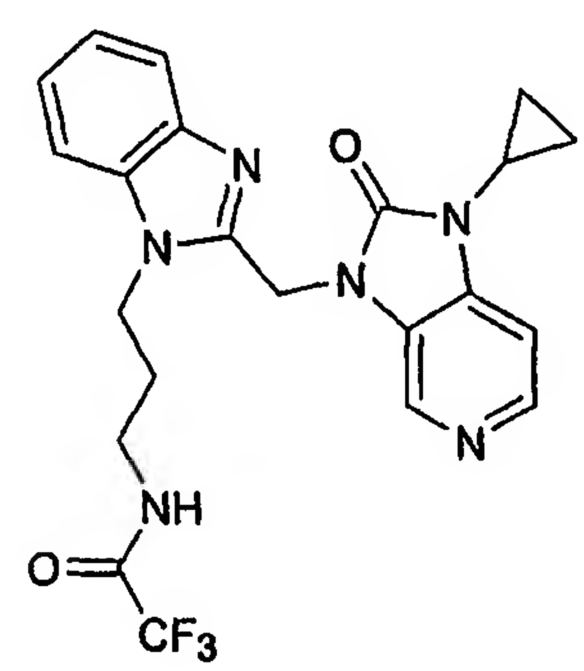
Example 50



A mixture of Example **49** (0.050 g, 0.14 mmol) and polystyrene diisopropylethylamine resin (PS-DIEA resin, Argonaut, 0.075 g, 0.28 mmol) in anhydrous CH_2Cl_2 (1 mL) was treated with acetic anhydride (0.141 g, 1.38 mmol) and stirred at room temperature for 18 hours. Solids which precipitated from solution were redissolved by the addition of chloroform (1 mL), and the reaction mixture was filtered to remove the resin. The filtrate was concentrated *in vacuo*, and the residue was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.074 g (>100% yield) of the trifluoroacetic acid salt of Example **50** as a glassy, colorless solid.

^{1}H NMR (DMSO-d_6) δ 0.99-1.02 (m, 2 H), 1.13-1.17 (m, 2 H), 1.84 (s, 3 H), 1.95 (t, J = 7.3 Hz, 2 H), 3.14-3.17 (m, 3 H), 4.41 (t, J = 7.5 Hz, 2 H), 5.57 (s, 2 H), 7.25 (t, J = 7.4 Hz, 1 H), 7.33 (t, J = 7.4 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.68 (d, J = 8.1 Hz, 1 H), 7.83 (d, J = 6.4 Hz, 1 H), 7.99 (t, J = 5.2 Hz, 1 H), 8.62 (d, J = 6.2 Hz, 1 H), 8.83 (s, 1 H);
MS m/e 405 (MH^+).

Example 51

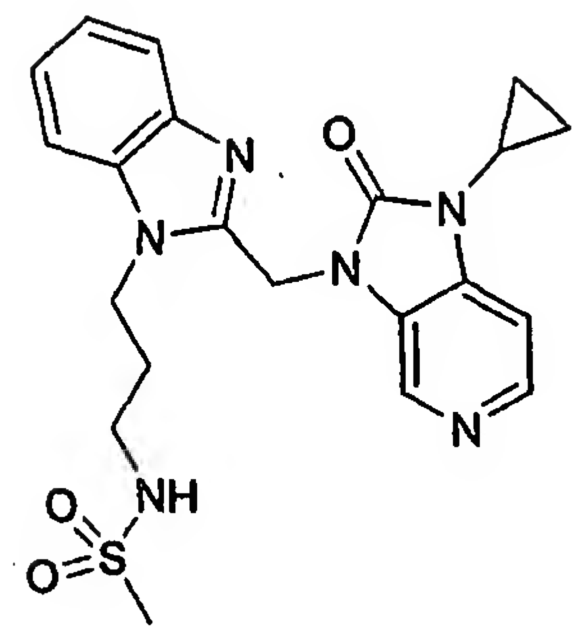


Example **51** was prepared according to the same procedure described for Example **50** using trifluoroacetic anhydride.

^{1}H NMR (DMSO-d_6) δ 0.98-1.01 (m, 2 H), 1.13-1.17 (m, 2 H), 2.03-2.08 (m, 2 H), 3.14-3.18 (m, 1 H), 3.33-3.37 (m, 2 H), 4.42 (t, J =7.5 Hz, 2 H), 5.54 (s, 2 H), 7.20-7.23 (m, 1 H), 7.29-7.23 (m, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.1

Hz, 1 H), 7.81 (d, J = 6.3 Hz, 1 H), 8.61 (d, J = 6.3 Hz, 1 H), 8.81 (s, 1 H), 9.54-9.56 (m, 1 H);
MS m/e 459 (MH^+).

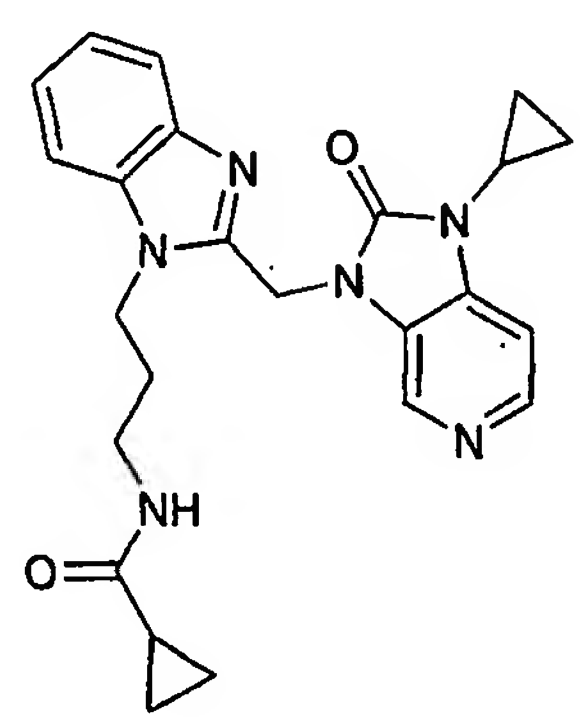
Example 52



Example **52** was prepared according to the same procedure described for Example **50** using methanesulfonyl chloride.

^{1}H NMR (DMSO-d_6) δ 1.04-1.07 (m, 2 H), 1.14-1.17 (m, 2 H), 2.12 (t, J = 7.4 Hz, 2 H), 2.96 (s, 3 H), 3.16-3.18 (m, 3 H), 4.58 (t, J = 7.6 Hz, 2 H), 5.82 (s, 2 H), 7.23-7.25 (m, 1 H), 7.47 (t, J = 7.6 Hz, 1 H), 7.54 (t, J = 7.7 Hz, 1 H), 7.75 (d, J = 8.1 Hz, 1 H), 7.88 (d, J = 6.5 Hz, 1 H), 7.94 (d, J = 8.3 Hz, 1 H), 8.66 (d, J = 6.5 Hz, 1 H), 8.90 (s, 1 H);
MS m/e 441 (MH^+).

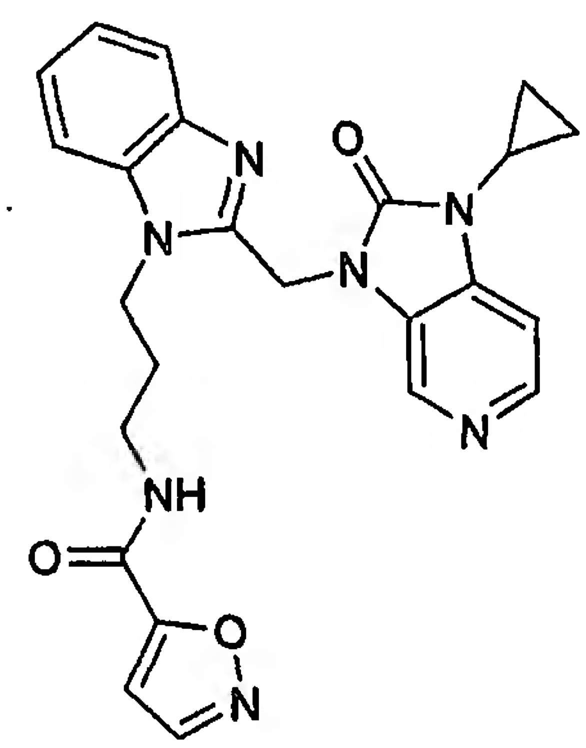
Example 53



Example **53** was prepared according to the same procedure described for Example **50** using cyclopropanecarbonyl chloride.

^{1}H NMR (DMSO-d_6) δ 0.63-0.69 (m, 4 H), 0.98-1.02 (m, 2 H), 1.13-1.17 (m, 2 H), 1.53-1.58 (m, 1 H), 1.94-2.00 (m, 2 H), 3.14-3.20 (m, 3 H), 4.40 (t, J = 7.4 Hz, 2 H), 5.55 (s, 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.31 (t, J = 7.5 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.82 (d, J = 6.3 Hz, 1 H), 8.21 (t, J = 5.1 Hz, 1 H), 8.61 (d, J = 6.2 Hz, 1 H), 8.82 (s, 1 H);
MS m/e 431 (MH^+).

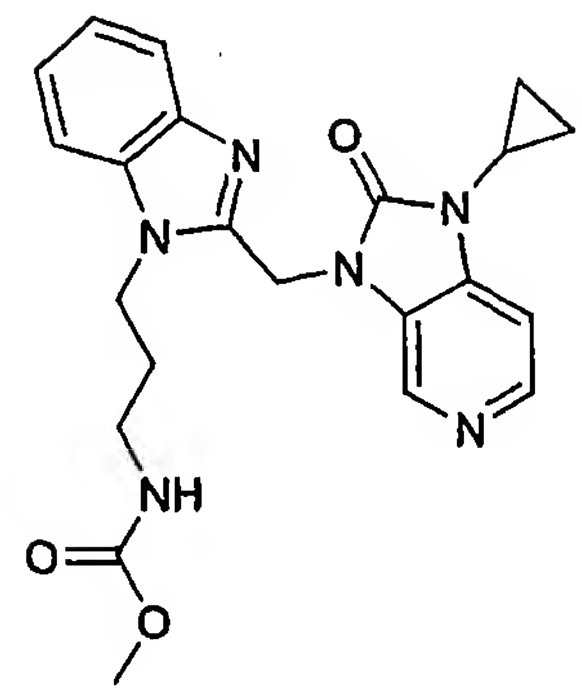
Example 54



Example **54** was prepared according to the same procedure described for Example **50** using isoxazole-5-carbonyl chloride.

^{1}H NMR (DMSO-d_6) δ 0.97-1.00 (m, 2 H), 1.12-1.16 (m, 2 H), 2.06-2.12 (m, 2 H), 3.13-3.17 (m, 1 H), 3.39-3.43 (m, 2 H), 4.46 (t, J = 7.5 Hz, 2 H), 5.56 (s, 2 H), 7.06 (s, 1 H), 7.22 (t, J = 7.4 Hz, 1 H), 7.30 (t, J = 7.4 Hz, 1 H), 7.56 (d, J = 8.1 Hz, 1 H), 7.67 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.3 Hz, 1 H), 8.60 (d, J = 6.2 Hz, 1 H), 8.75 (s, 1 H), 8.81 (s, 1 H), 9.08 (t, J = 5.5 Hz, 1 H);
MS m/e 458 (MH^+).

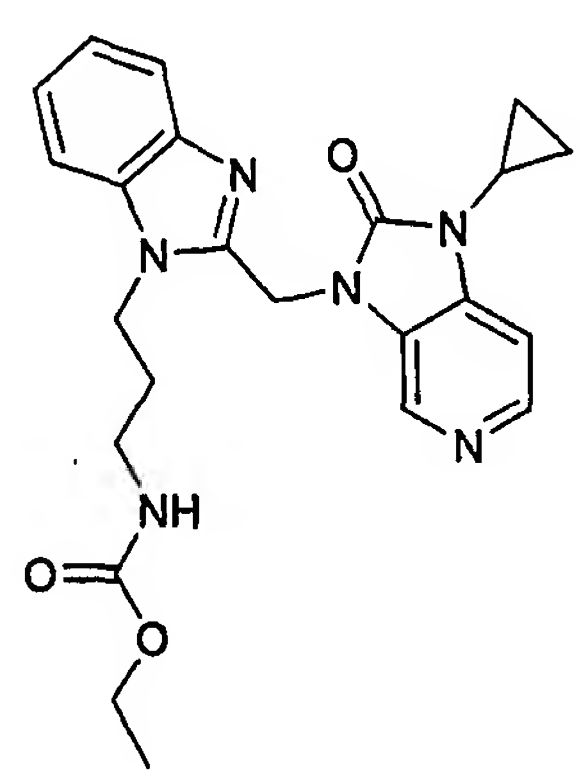
Example 55



Example **55** was prepared according to the same procedure described for Example **50** using methyl chloroformate.

^{1}H NMR (DMSO-d_6) δ 0.90-0.93 (m, 2 H), 1.03-1.09 (m, 2 H), 1.80-1.86 (m, 2 H), 2.98-3.02 (m, 1 H), 3.05-3.08 (m, 2 H), 3.53 (s, 3 H), 4.35 (t, J = 7.5 Hz, 2 H), 5.38 (s, 2 H), 7.17 (t, J = 7.7 Hz, 1 H), 7.23-7.29 (m, 3 H), 7.57 (d, J = 8.2 Hz, 2 H), 8.25 (d, J = 5.0 Hz, 1 H), 8.40 (s, 1 H);
MS m/e 421 (MH^+).

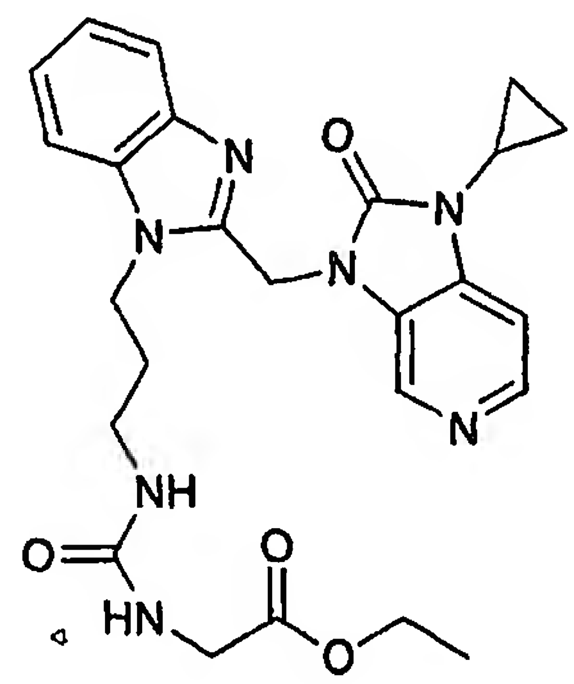
Example 56



Example **56** was prepared according to the same procedure described for Example **50** using ethyl chloroformate.

^{1}H NMR (DMSO-d_6) δ 0.89-0.94 (m, 2 H), 1.03-1.09 (m, 2 H), 1.16 (t, J = 7.1 Hz, 3 H), 1.80-1.86 (m, 2 H), 2.98-3.03 (m, 1 H), 3.04-3.08 (m, 2 H), 4.00 (q, J = 7.1 Hz, 2 H), 4.35 (t, J = 7.5 Hz, 2 H), 5.39 (s, 2 H), 7.23-7.29 (m, 3 H), 7.29 (d, J = 5.2 Hz, 1 H), 7.57 (d, J = 8.8 Hz, 2 H), 8.25 (d, J = 5.1 Hz, 1 H), 8.40 (s, 1 H); MS m/e 435 (MH^+).

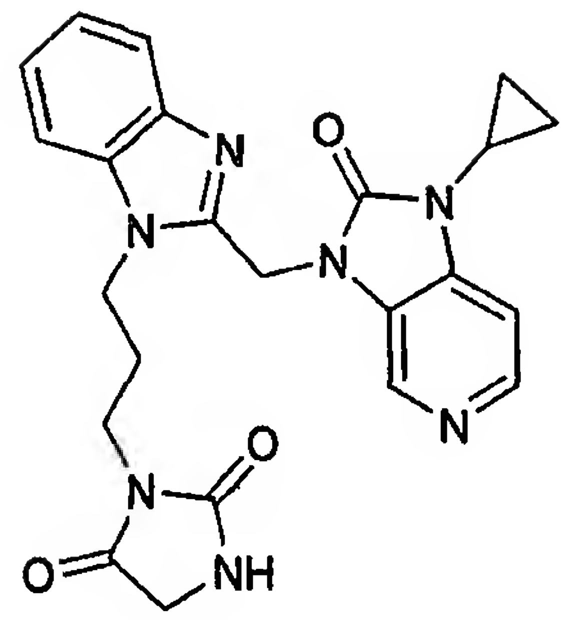
Example 57



A solution of Example **49** (0.050 g, 0.14 mmol) in chloroform (2 mL) was treated with ethyl isocyanatoacetate (0.018 g, 0.14 mmol) and stirred for 15 minutes at room temperature. The mixture was concentrated *in vacuo*. The residue was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.080 g (96 % yield) of the trifluoroacetic acid salt of Example **57** as a glassy, colorless solid.

^{1}H NMR (DMSO-d_6) δ 0.98-1.02 (m, 2 H), 1.13-1.17 (m, 5 H), 1.91-1.97 (m, 2 H), 3.10-3.12 (m, 2 H), 3.15-3.18 (m, 1 H), 3.76 (s, 2 H), 4.04 (q, J = 7.1 Hz, 2 H), 4.39 (t, J = 7.5 Hz, 2 H), 5.55 (s, 2 H), 6.31 (bs, 1 H), 6.43 (bs, 1 H), 7.23 (t, J = 7.6 Hz, 1 H), 7.29-7.33 (m, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.66 (d, J = 8.1 Hz, 1 H), 7.83 (d, J = 6.3 Hz, 1 H), 8.62 (d, J = 5.8 Hz, 1 H), 8.83 (s, 1 H);
MS m/e 492 (MH^+).

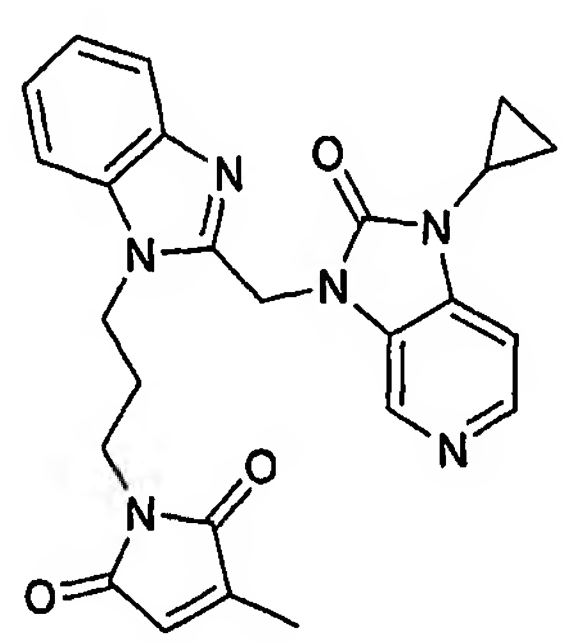
Example 58



Example **57** (0.061 g, 0.14 mmol) was dissolved in glacial acetic acid (2 mL) and the resulting solution was heated to 120 °C in a sealed tube for several hours. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.036 g (47 % yield) of the trifluoroacetic acid salt of Example **58** as a glassy, colorless solid.

^{1}H NMR (DMSO-d_6) δ 0.98-1.01 (m, 2 H), 1.13-1.17 (m, 2 H), 2.01-2.07 (m, 1 H), 3.13-3.18 (m, 2 H), 3.52 (t, J = 6.8 Hz, 2 H), 3.92 (s, 2 H), 4.38-4.43 (m, 2 H), 5.55 (s, 2 H), 7.24 (t, J = 7.6 Hz, 1 H), 7.29-7.33 (m, 1 H), 7.56-7.59 (m, 1 H), 7.67 (d, J = 8.0 Hz, 1 H), 7.81-7.83 (m, 1 H), 8.09 (s, 1 H), 8.60-8.62 (m, 1 H), 8.80-8.82 (m, 1 H);
MS m/e 446 (MH^+).

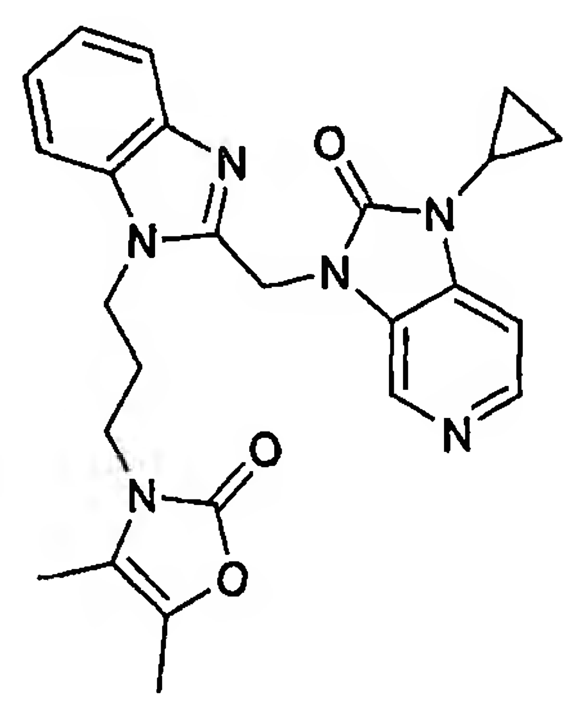
Example 59



Example **49** (0.050 g, 0.14 mmol) was combined with citraconic anhydride (0.017 g, 0.15 mmol) and glacial acetic acid (2 mL). The resulting mixture was heated to 80 °C for 18 hours and then concentrated *in vacuo*. Purification by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) gave 0.052g (66 % yield) of the trifluoroacetic acid salt of Example **59** as a glassy, colorless solid.

^{1}H NMR (DMSO-d_6) δ 0.97-1.00 (m, 2 H), 1.12-1.16 (m, 2 H), 2.00 (s, 3 H), 2.00-2.06 (m, 2 H), 3.12-3.17 (m, 1 H), 3.56 (t, J = 6.8 Hz, 2 H), 4.40 (t, J = 7.7 Hz, 2 H), 5.51 (s, 2 H), 6.62-6.63 (m, 1 H), 7.22 (t, J = 7.4 Hz, 1 H), 7.29 (t, J = 7.3 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.1 Hz, 1 H), 7.80 (d, J = 6.2 Hz, 1 H), 8.59 (d, J = 4.7 Hz, 1 H), 8.80 (s, 1 H);
MS m/e 457 (MH^+).

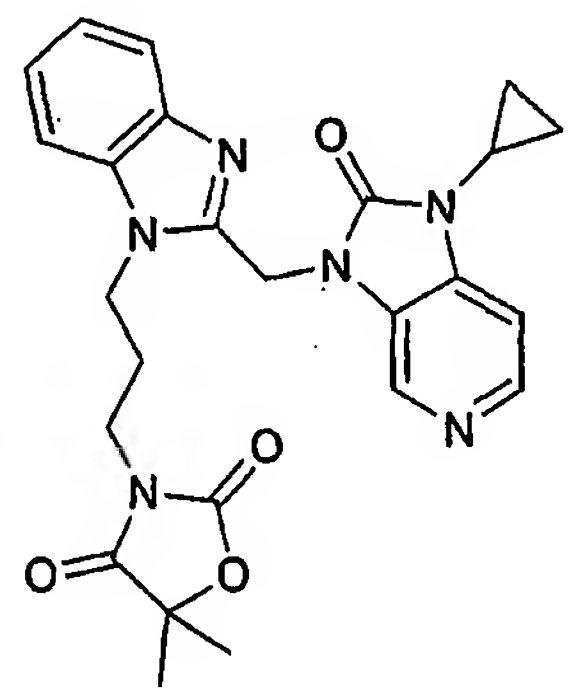
Example 60



Example **49** (0.050g, 0.14 mmol) was combined with 4,5-dimethyl-1,3-dioxo-2-one (0.016 g, 0.14 mmol), sodium bicarbonate (0.024 g, 0.14 mmol) and anhydrous DMF (2 mL), and the resulting mixture was stirred at room temperature for 18 hours. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.029 g (37 % yield) of the trifluoroacetic acid salt of Example **60** as a glassy, colorless solid.

^{1}H NMR (DMSO-d_6) δ 0.98-1.00 (m, 2 H), 1.13-1.17 (m, 2 H), 1.96 (s, 3 H), 2.00 (s, 3 H), 2.06-2.12 (m, 2 H), 3.13-3.18 (m, 1 H), 3.61 (t, J = 7.3 Hz, 2 H), 4.44 (t, J = 7.7 Hz, 2 H), 5.54 (s, 2 H), 7.22 (t, J = 7.3 Hz, 1 H), 7.30 (t, J = 7.3 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.0 Hz, 1 H), 8.61 (d, J = 5.3 Hz, 1 H), 8.81 (s, 1 H);
MS m/e 459 (MH^+).

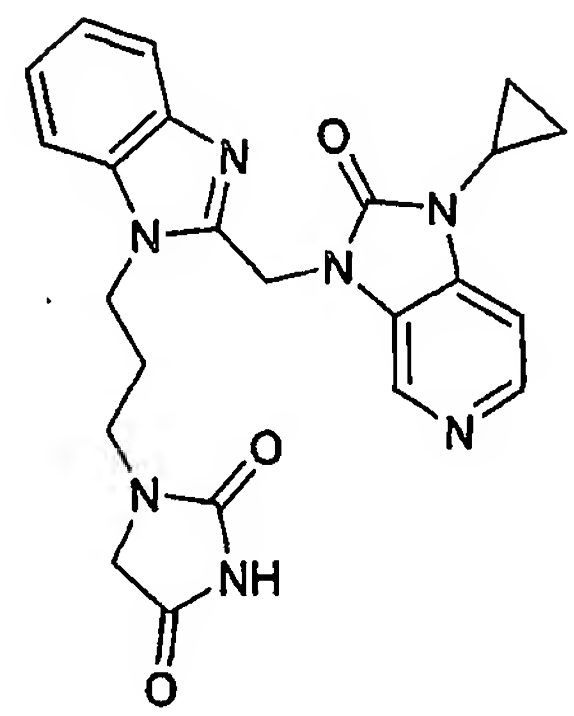
Example 61



Example **49** (0.050 g, 0.14 mmol) was combined with methyl-2-hydroxyisobutyrate (0.018 g, 0.14 mmol), a catalytic amount of 50 % sodium methoxide in MeOH and diethyl carbonate (1 mL) in a sealed tube and the mixture was heated to 175 °C for 18 hours. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.018 g (21 % yield) of the trifluoroacetic acid salt of Example **61** as a glassy, colorless solid.

^{1}H NMR (DMSO-d_6) δ 0.99-1.01 (m, 2 H), 1.13-1.15 (m, 2 H), 1.52 (s, 6 H), 2.11 (t, J = 7.5 Hz, 2 H), 3.14-3.16 (m, 1 H), 3.60 (t, J = 6.9 Hz, 2 H), 4.46 (t, J = 7.7 Hz, 2 H), 5.54 (s, 2 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.31 (t, J = 7.5 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.1 Hz, 1 H), 8.61 (s, 1 H), 8.81 (s, 1 H);
MS m/e 475 (MH^+).

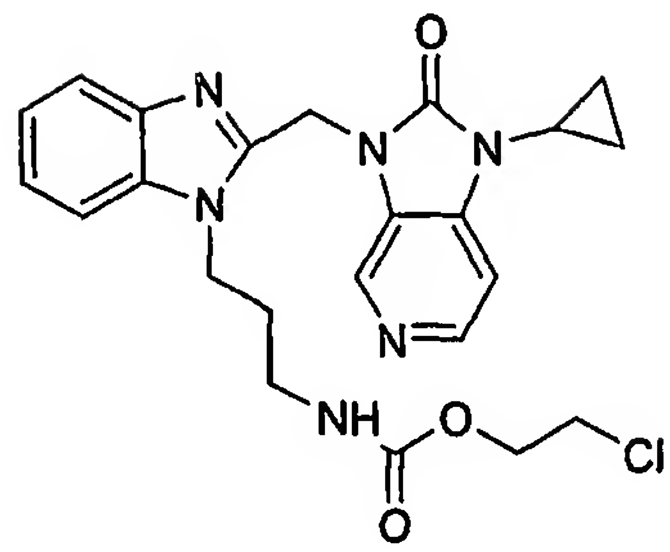
Example 62



Example **49** (0.050 g, 0.14 mmol) was combined with N-chloroacetyl urethane (0.024 g, 0.14 mmol), sodium bicarbonate (0.023g, 0.28 mmol) and anhydrous acetonitrile (2 mL) in a sealed tube. The mixture was heated to 140 °C for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) to give 0.030 g (39 % yield) of the trifluoroacetic acid salt of Example **62** as a glassy, colorless solid.

^{1}H NMR (DMSO-d_6) δ 0.98-1.01 (m, 2 H), 1.13-1.17 (m, 2 H), 2.00-2.06 (m, 2 H), 3.13-3.18 (m, 1 H), 3.41 (t, J = 6.8 Hz, 2 H), 4.00 (s, 2 H), 4.41 (t, J = 7.7 Hz, 2 H), 5.56 (s, 2 H), 7.22 (t, J = 7.6 Hz, 1 H), 7.30 (t, J = 7.3 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.71 (d, J = 8.1 Hz, 1 H), 7.81 (d, J = 6.3 Hz, 1 H), 8.60 (d, J = 6.0 Hz, 1 H), 8.80 (s, 1 H), 10.77 (s, 1 H);
MS m/e 446 (MH^+).

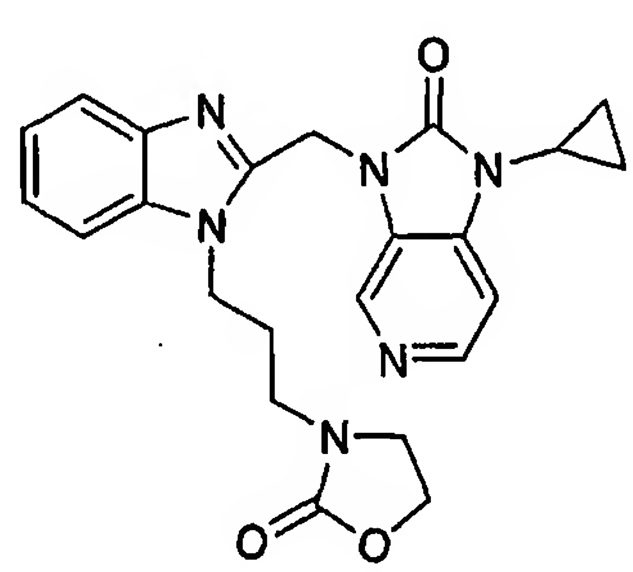
Example 63



A mixture of Example **49** (100 mg, 0.27 mmol) and 2-bromoethylchloroformate (51.7 mg, 0.27 mmol) was stirred at room temperature for 18 hours. The reaction mixture was filtered to remove inorganic impurities and the solid was washed with MeOH. The MeOH solution was concentrated to give 126 mg (99% yield) of Example **63** as a hygroscopic solid.

^{1}H NMR (DMSO-d_6) δ 0.94 (bs, 2 H), 1.10 (d, J = 5.4 Hz, 2 H), 1.21 (d, J = 6.4 Hz, 2 H), 1.86-1.89 (m, 2 H), 3.09-3.11 (m, 1 H), .3.78-3.80 (m, 1 H), 3.85-3.87 (m, 1 H), 4.21-4.23 (m, 2 H), 4.35-4.37 (m, 2 H), 5.43 (s, 2 H), 7.18 (t, J = 7.7 Hz, 1 H), 7.25 (t, J = 7.5 Hz, 1 H), 7.46-7.50 (m, 2 H), 7.55-7.60 (m, 1 H), 8.37 (d, J = 5.0 Hz, 1 H), 8.54 (s, 1 H);
MS m/e 469 (MH^+).

Example 64

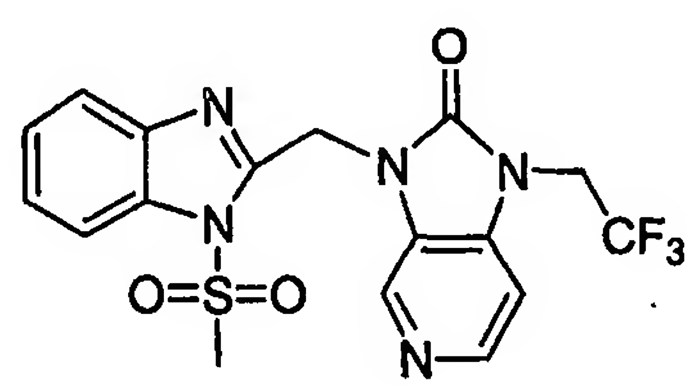


A mixture of Example **63** (70 mg, 0.149 mmol) and lithium bis(trimethylsilyl)amide (0.15 mL, 0.149 mmol) was stirred at reflux in dioxane

(15 mL) for 16 hours. The solvent was evaporated and the residue was diluted with EtOAc, washed with H_2O, dried over Na_2SO_4, and evaporated to give 41 mg (63% yield) of Example **64**.

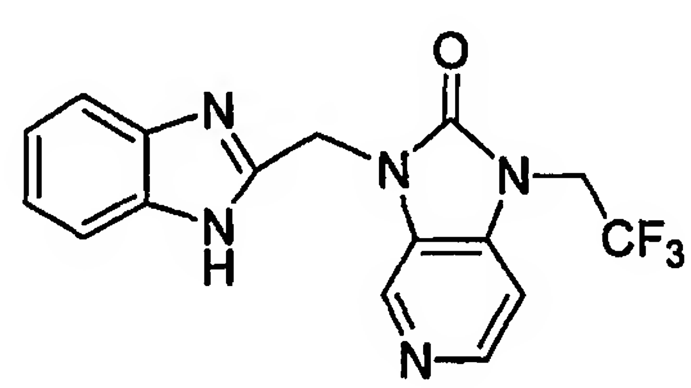
^{1}H NMR (DMSO-d_6) δ 0.90-0.93 (m, 2 H), 1.01-1.09 (m, 2 H), 1.92-1.98 (m, 2 H), 2.98-3.03 (m, 1 H), 3.27 (t, J = 6.9 Hz, 2 H), 3.55 (t, J = 8.1 Hz, 2 H), 4.27 (t, J = 7.7 Hz, 2 H), 4.37 (t, J = 7.7 Hz, 2 H), 5.40 (s, 2 H), 7.17-7.20 (t, J = 7.4 Hz, 1 H), 7.22-7.29 (m, 2 H), 7.56-7.62 (m, 2 H), 8.25 (d, J = 5.3 Hz, 1 H), 8.42 (s, 1 H); MS m/e 416 (MH^+).

Example 65



MS m/e 426 (MH^+).

Example 66

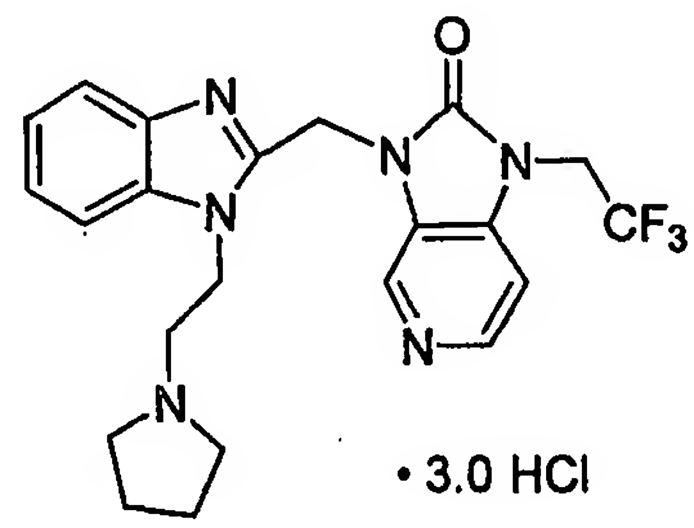


Example **65** was refluxed with hydrazine hydrate (5 mL) in MeOH (10 mL) for 1 hour. The solvent was evaporated and the oily residue was diluted with water and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and evaporated to give 467 mg (29% yield) of Example **66**.

^{1}H NMR (DMSO-d_6) δ 4.91 (q, J = 9.3 Hz, 2 H), 5.38 (s, 2 H), 7.12-7.21 (m, 2 H), 7.44 (d, J = 5.3 Hz, 1 H), 7.45-7.50 (m, 1 H), 7.51-7.58 (m, 1 H), 8.32 (d, J = 5.3 Hz, 1 H), 8.38 (s, 1 H), 12.60 (s, 1 H);

MS m/e 348 (MH^+).

Example 67



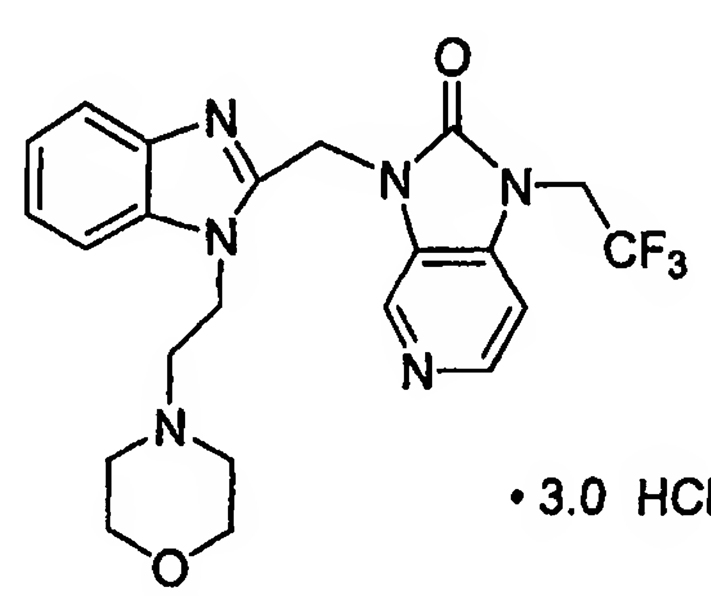
• 3.0 HCl

^{1}H NMR (DMSO-d_6) δ 1.88-2.01 (m, 2 H), 2.01-2.13 (m, 2 H), 3.10-3.22 (m, 2 H),.3.58-3.65 (m, 2 H), 3.70-3.79 (m, 2 H), 4.90-4.99 (m, 2 H), 5.10-5.23 (m, 2 H), 5.95 (s, 2 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 8.08 (d, J = 6.1 Hz, 1 H), 8.76 (d, J = 6.4 Hz, 1 H), 9.18 (s, 1 H);

IR (KBr, cm^{-1}) 3416, 2927, 1754, 1653, 1627, 1518, 1462, 1264, 1168, 1121, 831, 755.

MS m/e 445 (MH^+).

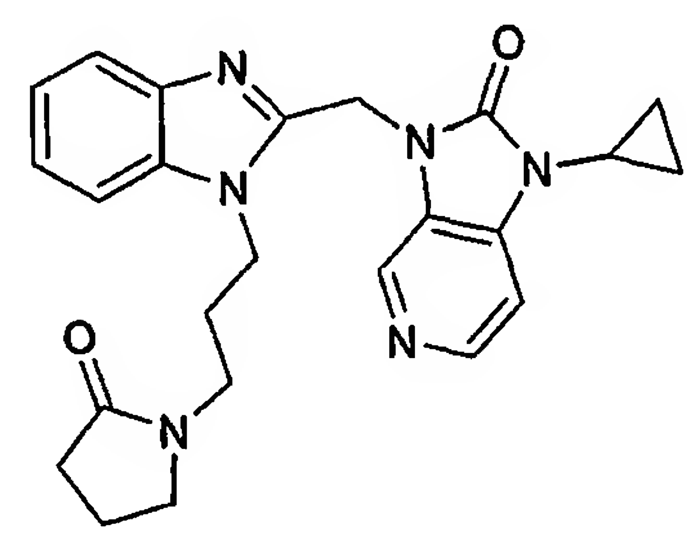
Example 68



• 3.0 HCl

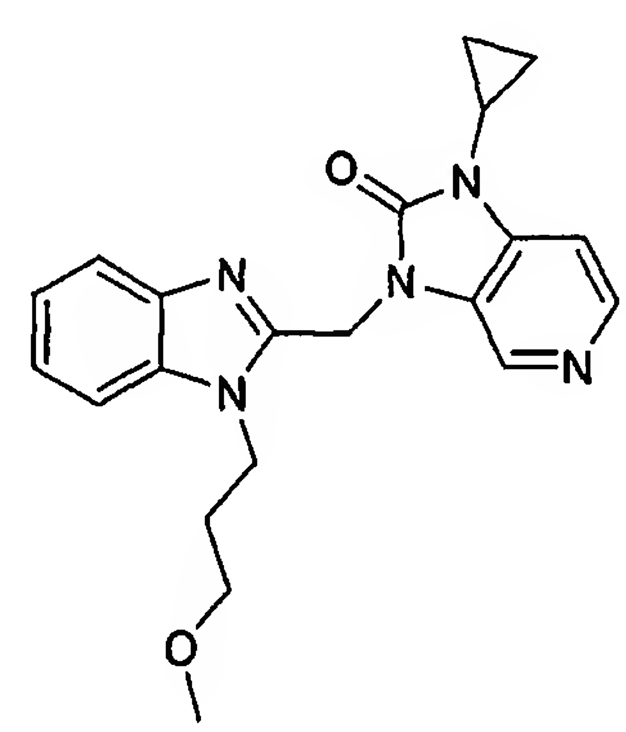
^{1}H NMR (DMSO-d_6) δ 3.19-3.31 (m, 2 H), 3.56-3.63 (m, 2 H), 3.65-3.74 (m, 2 H), 3.86-3.95 (m, 2 H), 4.00-4.09 (m, 2 H), 5.01 (t, J = 7.5 Hz, 2 H), 5.16 (q, J = 9.0 Hz, 2 H), 5.93 (s, 2 H), 7.34 (t, J = 7.6 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 1 H), 7.61 (d, J = 8.3 Hz, 1 H), 7.99 (d, J = 7.9 Hz, 1 H), 8.08 (d, J = 6.1 Hz, 1 H), 8.75 (d, J = 6.4 Hz, 1 H), 9.18 (s, 1 H);
IR (KBr, cm^{-1}) 3430, 1761, 1618, 1517, 1268, 1172, 823, 770;
MS m/e 461 (MH$^+$).

Example 69



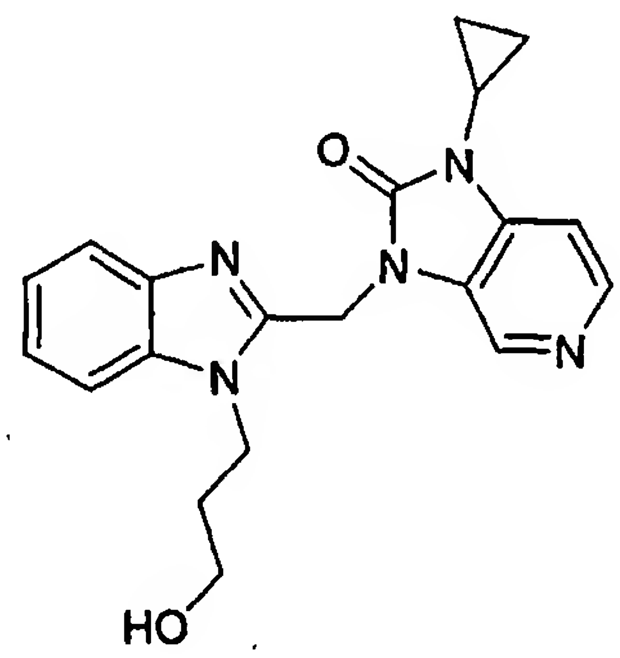
^{1}H NMR (DMSO-d_6) δ 1.03-1.08 (m, 2 H), 1.12-1.16 (m, 2 H), 2.01-2.17 (m, 2 H), 2.21-2.31 (m, 2 H), 2.31-2.41 (m, 2 H), 3.21-3.35 (m, 3 H), 3.40-50 (m, 1 H), 3.61-3.72 (m, 1 H), 4.45-4.51 (m, 2 H), 5.77(s, 2 H), 7.41-7.48 (m, 2 H), 7.67 (d, J = 8.1 Hz, 1 H), 7.85-7.88 (m, 2 H), 8.64 (d, J = 6.7 Hz, 1 H), 8.95 (s, 1 H);
MS m/e 430 (MH$^+$).

Example 70



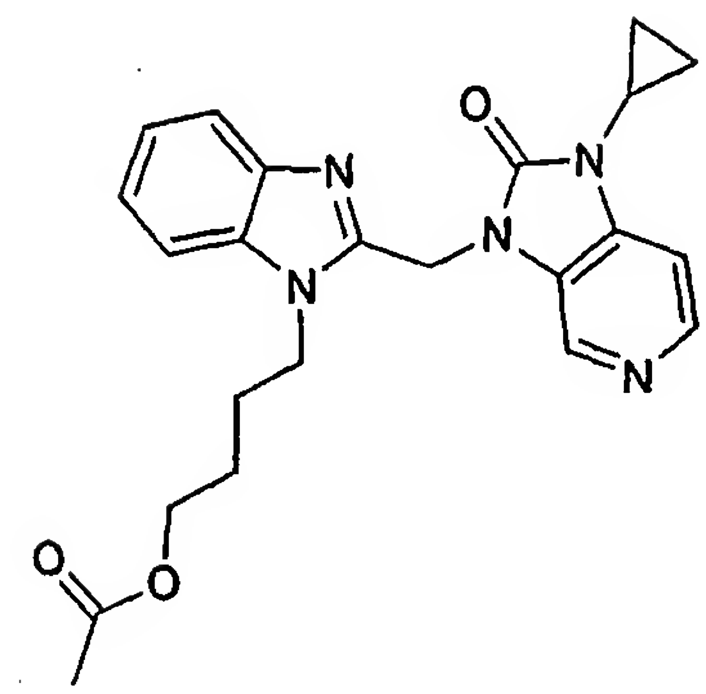
^{1}H NMR ($CDCl_3$) δ 1.14 (q, J = 7.5 Hz, 2 H), 1.21 (q , J = 6.4 Hz, 2 H), 2.20-2.23 (m, 2 H), 3.07 (m, 1 H), 3.38 (s, 3 H), 3.38 (t, J = 5.4 Hz, 2 H), 4.56 (t, J = 6.5 Hz, 2 H), 5.85 (s, 2 H), 7.40 (t, J = 7.6 Hz, 1 H), 7.45 (t, J = 7.7 Hz, 1 H), 7.53-7.55 (m, 2 H), 7.88 (d, J = 8.2 Hz, 1 H), 8.38 (d, J = 6.3 Hz, 1 H), 8.92 (s, 1 H); MS m/e 378 (MH^+).

Example 71



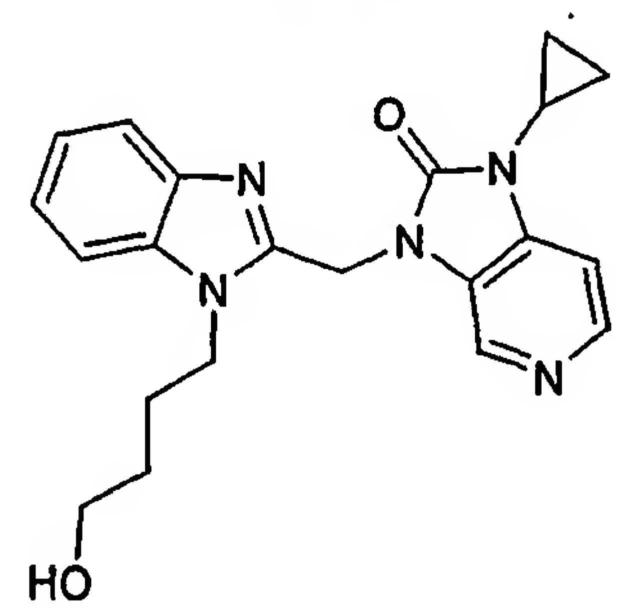
A solution of Example **70** (434 mg, 0.72 mmol) in CH_2Cl_2 (25 mL) was treated with boron tribromide (1M in CH_2Cl_2, 7.2 mL, 7.2 mmol). The reaction mixture was stirred at room temperature for 40 minutes and then was quenched slowly with anhydrous MeOH. The solvent was evaporated and the residue was diluted with MeOH and evaporated two more times. Purification by flash column chromatography (CH_2Cl_2/MeOH, 9:1) gave Example **71**.
^{1}H NMR (DMSO-d_6) δ 1.07 (d, J = 5.6 Hz, 2 H), 1.83 (t, J = 6.2 Hz, 2 H), 2.99 (t, J = 3.2 Hz, 1 H), 3.17 (d, J = 5.0 Hz, 1 H), 3.40 (t, J = 5.4 Hz, 2 H), 4.40 (t, J = 6.8 Hz, 2 H), 4.75 (t, J = 4.6, 1 H), 5.42 (s, 2 H), 7.16 (t, J = 7.5 Hz, 1 H), 7.24 (t, J = 7.6 Hz, 1 H), 7.29 (d, J = 4.8 Hz, 1 H), 7.56 (d, J = 8.1 Hz, 2 H), 8.25 (s, 1 H), 8.38 (s, 1 H); MS m/e 364 (MH^+).

Example 72



^1H NMR ($CDCl_3$) δ 0.99-1.03 (m, 2 H), 1.16-1.20 (m, 2 H), 1.65-1.69 (m,, 2 H), 1.71-1.75 (m, 2 H), 2.00 (s, 3 H), 2.92-2.95 (m, 1 H), 4.03 (t, J = 6.2 Hz, 2 H), 4.35 (t, J = 7.3 Hz, 2 H), 5.37 (s, 2 H), 7.14 (d, J = 5.0 Hz, 1 H), 7.26-7.32 (m, 3 H), 7.56-7.77 (m, 1 H), 8.32 (d, J = 5.4 Hz, 1 H), 8.72 (s, 1 H);
MS m/e 420 (MH^+).

Example 73



Example **72** (1.0 g, 2.48 mmol) and K_2CO_3 (1.03 g, 7.44 mmol) were stirred together in MeOH (5 mL) at room temperature for 1.5 hours. The mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 x 25 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated. The product was then recrystallized from MeOH to give 650 mg (70% yield) of Example **73**. Example **73** was converted to the HCl salt by treating a solution of **73** in MeOH with 4 N HCl in dioxane and then by evaporating the solvent.

^1H NMR (DMSO-d_6) δ 1.03-1.06 (m, 2 H), 1.12-1.16 (m, 2 H), 1.50-1.56 (m, 2 H), 1.89-1.83 (m, 2 H), 3.13-3.17 (m, 1 H), 3.46 (t, J = 6.3 Hz, 2 H), 4.46 (t, J = 7.5 Hz, 2 H), 5.70 (s, 2 H), 7.32 (t, J = 7.3 Hz, 1 H), 7.39 (t, J = 7.5 Hz, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 7.81 (d, J = 6.4 Hz, 1 H), 8.61 (d, J = 6.4 Hz, 1 H), 8.93 (s, 1 H);

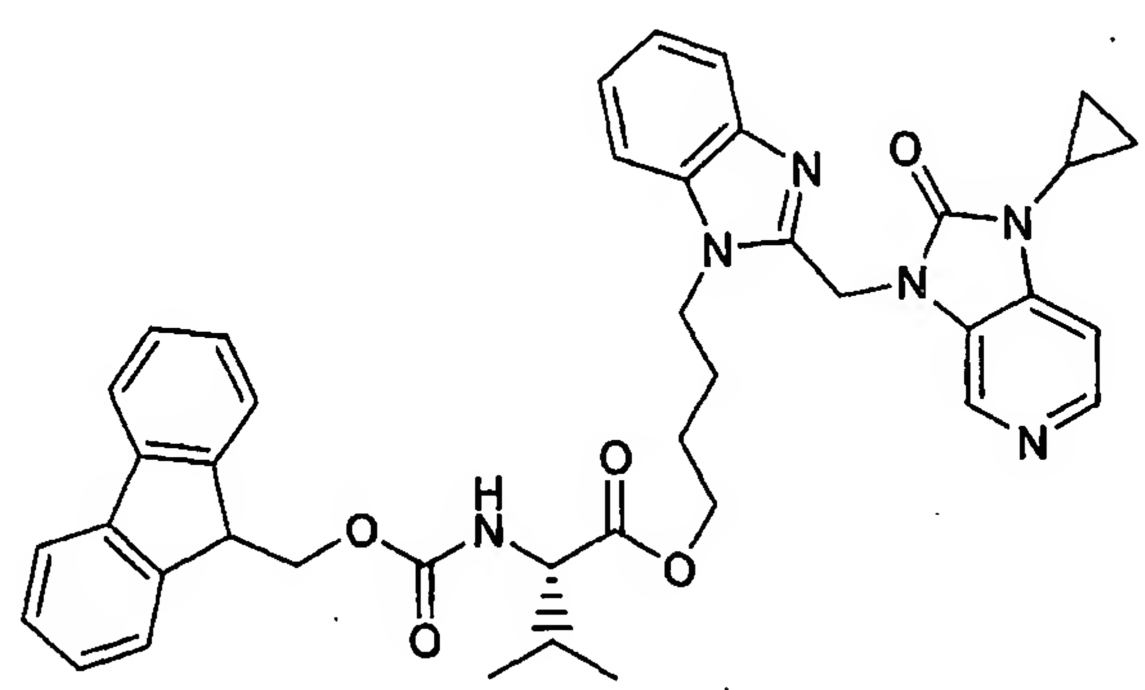
IR (KBr, cm^{-1}) 3350, 2907, 2443,1736, 1516, 1421, 1172, 825;

MS m/e 378 (MH^+).

Anal. Calcd for $C_{29}H_{30}N_4O_3$•1.25 HCl: C, 59.63; H, 5.78; N, 16.56

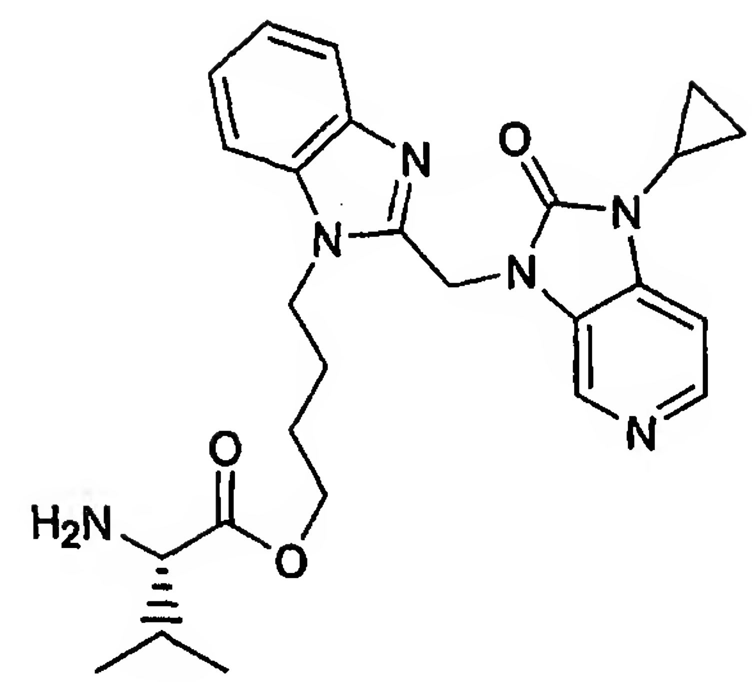
Found: C, 59.52; H, 5.88; N, 16.57.

Example 74



Fmoc-L-valine (0.690 g, 2.00 mmol) was combined with oxalyl chloride (0.508 g, 4.00 mmol) and dichloromethane (10 mL), and the resulting solution was stirred for 2 hours. The mixture was concentrated *in vacuo* to a yellow oil, which was then combined with Example **73** (0.252 g, 0.667 mmol) in dry CH_3CN (15 mL). The resulting mixture was stirred for 72 hours, then was diluted with H_2O (5 mL) and was concentrated *in vacuo* . The mixture was redissolved in EtOAc (50 mL) and the solution was washed successively with saturated aqueous $NaHCO_3$ (3 x 10 mL) and brine (10 mL). The aqueous extracts were combined and back-extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* Purification of the crude material by flash chromatography (CH_2Cl_2:MeOH, 25:1) gave 410 mg of Example **74** as an off-white solid which was used immediately upon isolation.

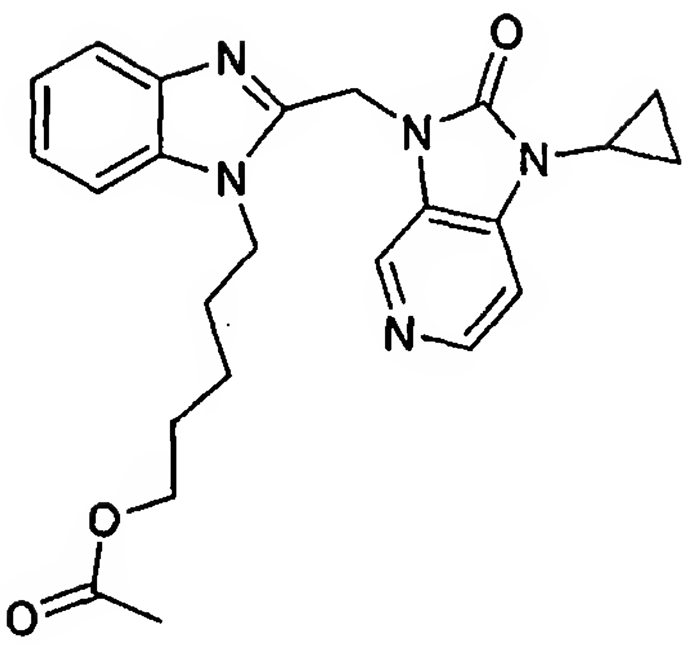
Example 75



A solution of Example **74** (410 mg) and piperidine (4 mL) in DMF (15 mL) was stirred for 18 hours. The mixture was concentrated *in vacuo*. The crude solid was redissolved in CH_2Cl_2 and filtered to remove insolubles. Purification of the crude product by flash chromatography (gradient, CH_2Cl_2:MeOH, 20:1 to 10:1) gave a 184 mg of an 85:15 mixture of Examples **75** and **73**. Repurification by preparative HPLC gave 284 mg (52 % yield) of pure Example **75** as the tris-trifluoroacetic acid salt.

^{1}H NMR (DMSO) δ 0.93 (d, J = 6.9 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.99-1.01 (m, 2 H), 1.13-1.17 (m, 2 H), 1.74-1.78 (m, 2 H), 1.86-1.92 (m, 2 H), 2.11-2.17 (m, 1 H), 3.13-3.17 (m, 1 H), 3.93 (br s, 1 H), 4.20-4.31 (m, 2 H), 4.44 (t, J = 7.4 Hz, 2 H), 5.56 (s, 2 H), 7.23 (dd, J = 7.5 Hz, 7.5 Hz, 1 H), 7.30 (dd, J = 7.5 Hz, 7.5 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.67 (d, J = 8.1 Hz, 1 H), 7.82 (d, J = 6.3 Hz, 1 H), 8.37 (br s, 2 H), 8.62 (d, J = 5.7 Hz, 1 H), 8.83 (s, 1 H);
MS m/e 477 (MH^+).

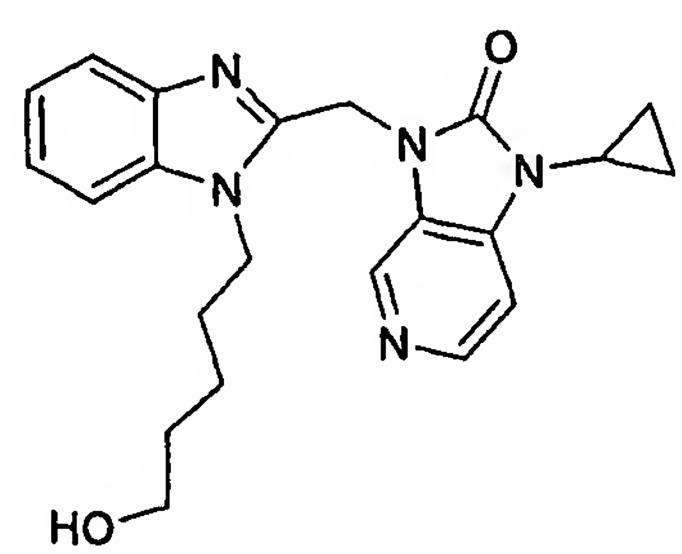
Example 76



^{1}H NMR (DMSO-d_6) δ 0.89-0.93 (m, 2 H), 1.06-1.08 (m, 2 H), 1.31-1.34 (m, 2 H), 1.54-1.58 (m, 2 H), 1.58-1.66 (m, 2 H), 1.98 (s, 3 H), 2.97-3.00 (m, 1 H), 3.96 (t, J = 6.6 Hz, 2 H), 4,32 (t, J = 7.5 Hz, 1 H), 5.39 (s, 2 H), 7.16 (t, J = 7.2 Hz, 1 H), 7.24 (t, J = 7.0 Hz, 1 H), 7.29 (d, J = 5.0 Hz, 1 H), 7.58 (t, J = 7.8 Hz, 2 H), 8.22 (bs, 1 H), 8.42 (bs, 1 H);

MS m/e 433 (MH^+).

Example 77



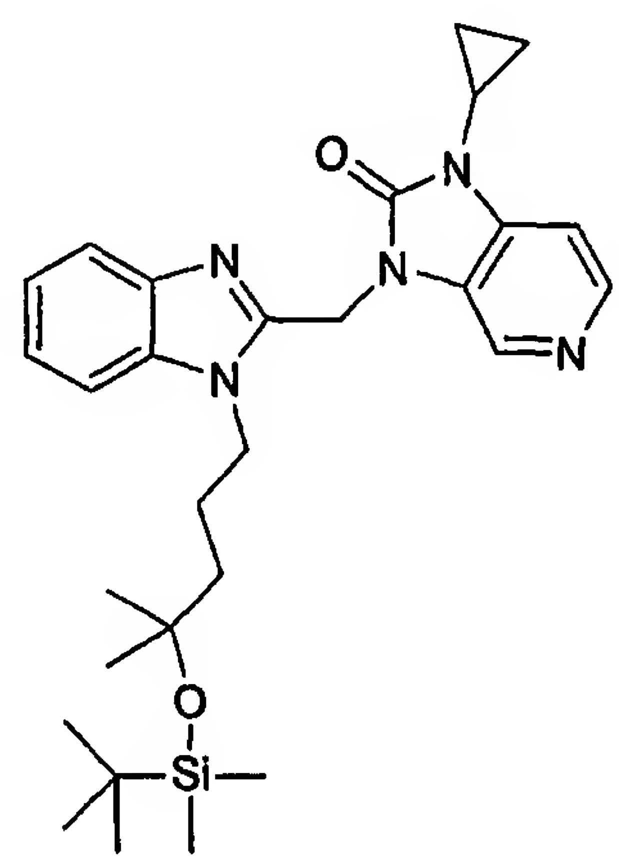
Example 76 (115 mg, 0.27 mmol) in 1 N HCl (20 mL) was heated to reflux for 1 hour then concentrated. The oily residue was triturated with EtOAc/MeOH to give 106 mg (94% yield) of Example 77 106 mg (94% yield) as the HCl salt.

^{1}H NMR (DMSO-d_6) δ 1.04-1.10 (m, 2 H), 1.10-1.17 (m, 2 H), 1.42-1.53 (m, 4 H), 1.85-1.91 (m, 2 H), 3.13-3.17 (m, 1 H), 3.40-3.50 (m, 2 H), 4.51 (t, J = 7.5 Hz,

2 H), 5.82 (s, 2 H), 7.43-7.46 (m, 1 H), 7.46-7.52 (m, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.85 (d, J = 6.4 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 8.64 (d, J = 6.4 Hz, 1 H), 8.97 (s, 1 H);

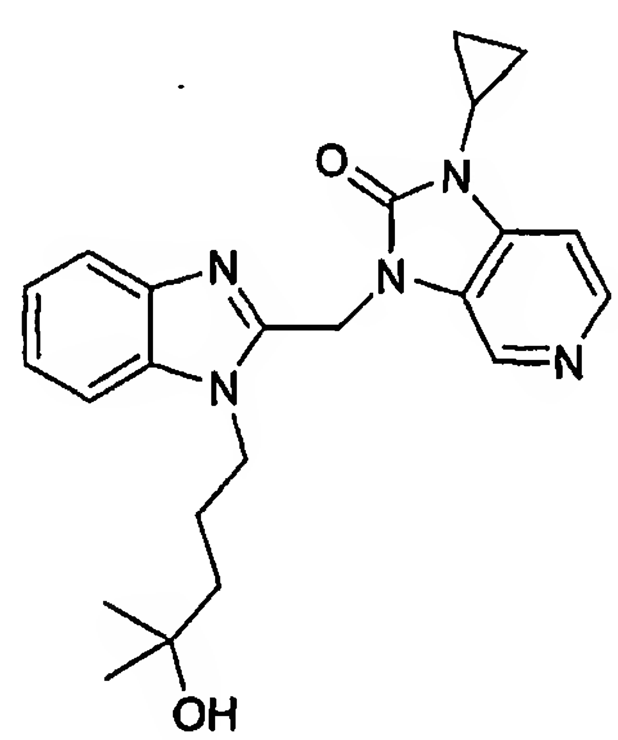
MS m/e 391 (MH^+).

Example 78



Example **78** was prepared according to the general coupling procedure shown in Scheme I-C and was used immediately upon isolation.

Example 79

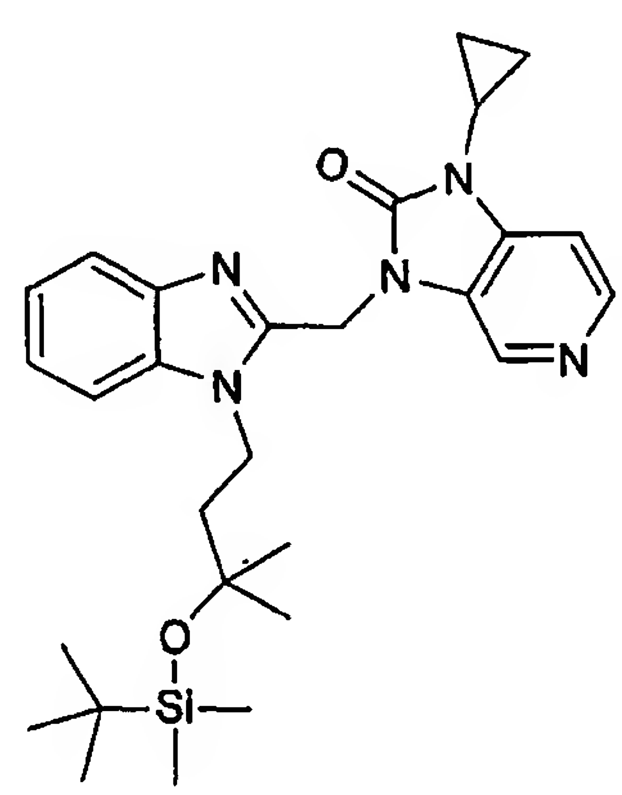


To a solution of Example **79** (86 mg, 0.17 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (TBAF, 1 M in THF, 0.25 mL, 0.25 mmol).

The reaction mixture was stirred at room temperature for 18 hours at which time more tetrabutylammonium fluoride (TBAF, 1 M in THF, 0.50 mL, 0.50 mmol) was added and stirring was continued at room temperature for an additional 18 hours. Purification by flash column chromatography (CH_2Cl_2/MeOH, 9:1) gave Example **79**.

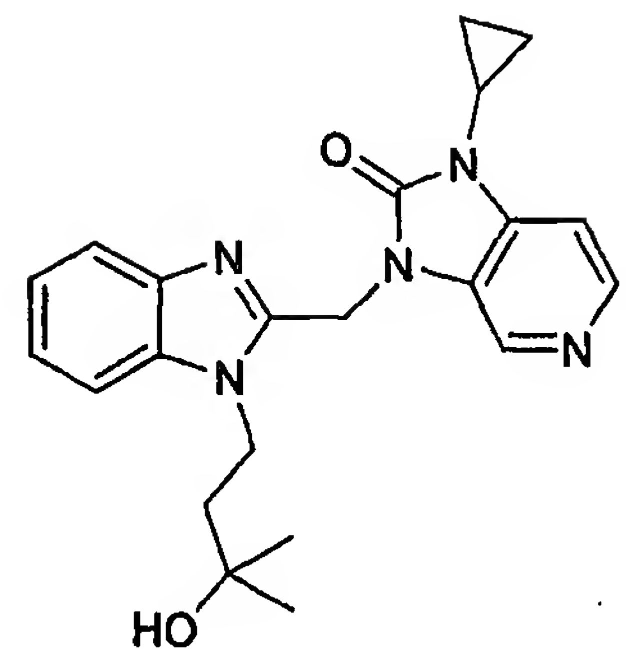
^{1}H NMR ($CDCl_3$) δ 0.94-0.97 (m, 2 H), 1.07 (s, 6 H), 1.09-1.11 (m, 2 H), 1.40 (t, J = 3.6 Hz, 2 H), 1.67-1.70 (m, 1 H), 2.86-2.87 (m, 1 H), 4.25 (t, J = 7.7 Hz, 2 H), 5.31 (s, 2 H), 7.05 (d, J = 5.3 Hz, 1 H), 7.18-7.21 (m, 2 H), 7.27 (t, J = 4.6 Hz, 1 H), 7.71 (t, J = 4.6 Hz, 1 H), 8.24 (d, J = 5.3 Hz, 1 H), 8.65 (s, 1 H);
IR (KBr, cm^{-1}) 3373, 2966, 1720, 1609, 1499, 1410, 913, 742;
MS m/e 406 (MH^+).

Example 80



Example **80** was prepared according to the general coupling procedure shown in Scheme I-C and was used immediately upon isolation.

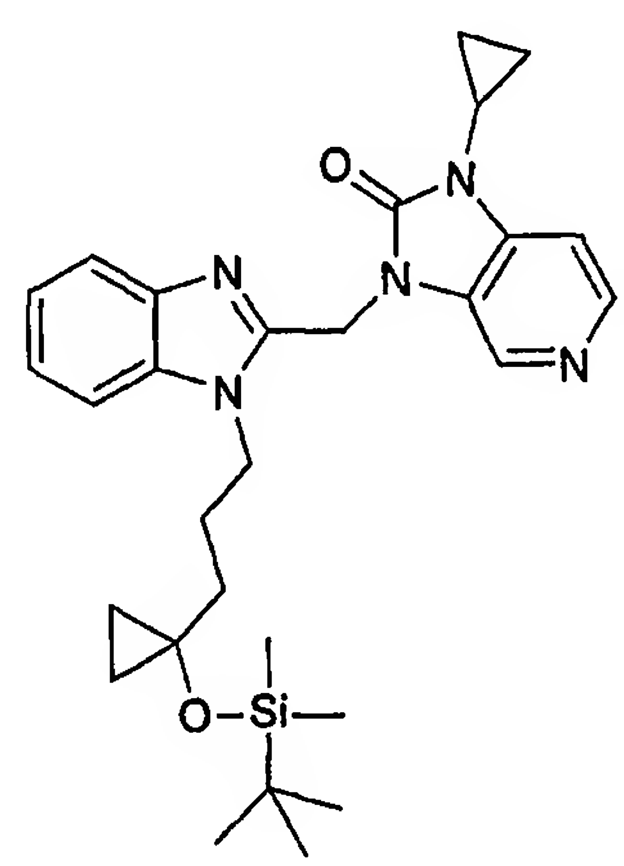
Example 81



Example **81** was prepared according to the same deprotection procedure as Example **79** from Example **80**.

^{1}H NMR ($CDCl_3$) δ 1.02-1.04 (m, 2 H), 1.16 (q, J = 6.9 Hz, 2 H), 1.32 (s, 6 H), 1.81 (t, J = 3.2 Hz, H), 2.49 (s, 1 H), 2.93 (m, 1 H), 4.45 (t, J = 3.4 Hz, 2 H), 5.41 (s, 2 H), 7.14 (d, J = 5.25 Hz, 1 H), 7.27-7.30 (m, 2 H), 7.33 (dd, J = 2.5, 3.5 Hz, 1 H), 7.77 (dd, J = 2.9, 3.1 Hz, 1 H), 8.34 (d, J = 5.3, 1 H), 8.77 (s, 1 H);
MS m/e 392 (MH^+).

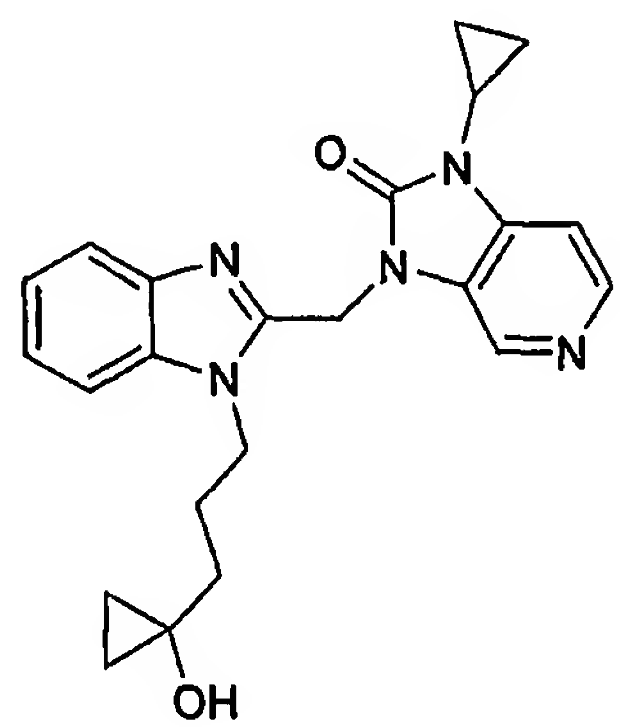
Example 82



^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6 H), 0.80-0.86 (m, 2 H), 0.89 (s, 9 H), 1.00-1.02 (m, 2 H), 1.15-1.17 (m, 2 H), 1.48-1.51 (m, 2 H), 1.77-1.86 (m, 2 H), 2.05 (t, J = 7.4

Hz, 2 H), 2.89-2.97 (m, 1 H), 4.29 (t, J = 7.4 Hz, 2 H), 5.35 (s, 2 H), 7.10 (d, J= 5.2 Hz, 1 H), 7.24-7.26 (m, 2 H), 7.31-7.33 (m, 1 H), 7.74-7.77 (m, 1 H), 8.31 (d, J = 5.2 Hz, 1 H), 8.69 (s, 1 H);
MS m/e 518 (MH^+).

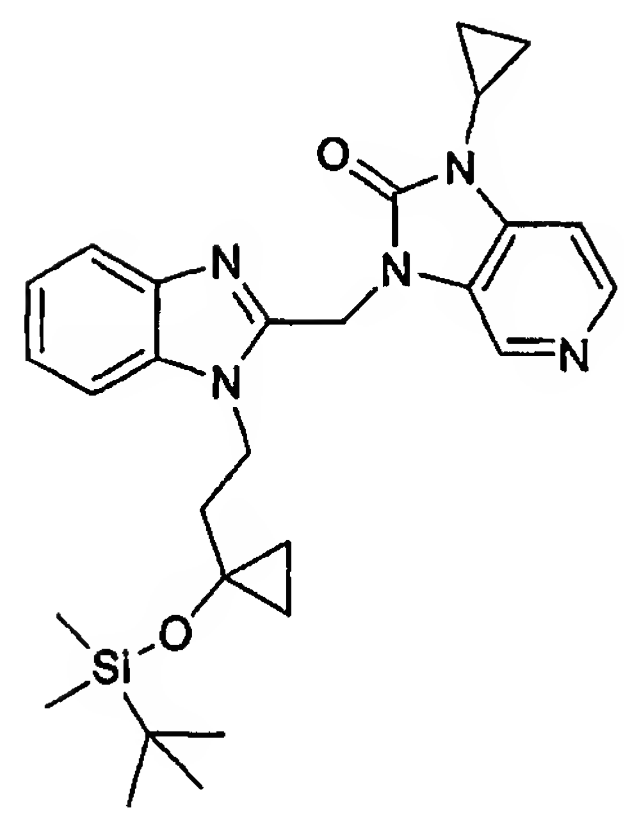
Example 83



Example **83** was prepared from Example **82** according to the same deprotection procedure described for Example **79**.

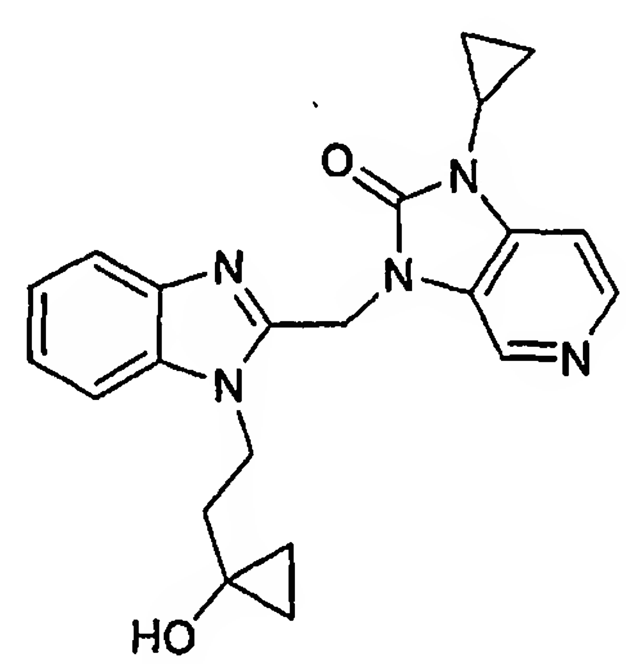
^{1}H NMR (DMSO-d_6) δ 0.91-1.05 (m, 4 H), 1.13-1.22 (m, 2 H), 1.77-1.84 (m, 2 H), 2.27 (q, J = 7.4 Hz, 2 H), 2.39 (t = 6.8 Hz, 2 H), 2.89-2.95 (m, 1 H), 4.23 (t, J = 7.7 Hz, 2 H), 5.27 (s, 2 H), 7.03 (d, J = 5.1 Hz, 1 H), 7.24-7.31 (m, 2 H), 7.34 (dd, J = 1.9, 6.4 Hz, 1 H), 7.66 (dd, J = 1.4, 7.1 Hz, 1 H), 8.23 (d, J = 5.2 Hz, 1 H), 8.60 (s, 1 H);
IR (KBr, cm^{-1}) 3392, 2938, 1721, 1609, 1499, 1410, 913, 743;
MS m/e 404 (MH^+).

Example 84



^{1}H NMR ($CDCl_3$) δ 0.05 (t, J = 5.8 Hz, 2 H), 0.14 (s, 6 H), 0.63 (t, J = 6.1 Hz, 2 H), 0.90 (s, 9 H), 1.00-1.03 (m, 2 H), 1.13-1.17 (m, 2 H), 1.86 (t, J = 6.6 Hz, 2 H), 2.89-2.92 (m, 1 H), 4.61 (t, J = 6.6 Hz, 2 H), 5.42 (s, 2 H), 7.12 (d, J = 4.9 Hz, 1 H), 7.22-7.24 (m, 2 H), 7.38-7.40 (m, 1 H), 7.72-7.74 (m, 1 H), 8.32 (d, J = 5.5 Hz, 1 H), 8.66 (s, 1 H);
MS m/e 504 (MH^+).

Example 85

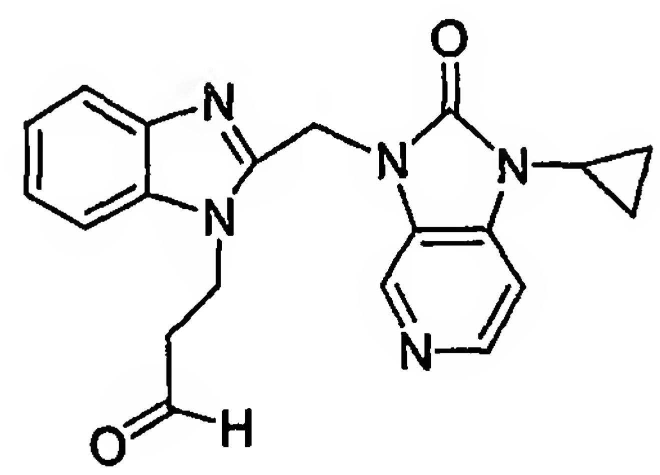


Example **85** was prepared from Example **84** according to the same deprotection procedure described for Example **79**.

^{1}H NMR (DMSO-d_6) δ 0.10 (q, J = 4.8 Hz, 2 H), 0.49 (q, J = 4.9 Hz, 2 H), 0.90-0.94 (m, 2 H), 1.04-1.07 (m, 2 H), 1.85 (t, J = 7.0 Hz, 2 H), 2.99 (m, 1 H), 4.54 (t,

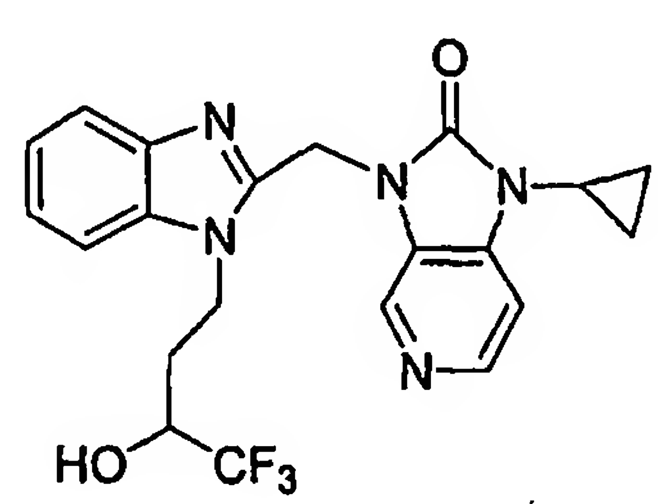
J = 7.0 Hz, 2 H), 5. 42 (s, 1 H), 5.46 (s, 2 H), 7.16 (dt, J = 1.0, 7.6 Hz, 1 H), 7.23 (dt, J = 1.0, 7.6 Hz, 1 H), 7.28 (d, J = 5.2 Hz, 1 H), 7.54 (dd, J = 8.0, 23.0 Hz, 2 H), 8.25 (d, J = 5.25 Hz. 1 H), 8.39 (s, 1 H);
MS m/e 390 (MH^+).

Example 86



To a solution of oxalyl chloride (326 mg, 2.57 mmol) in CH_2Cl_2 (5 mL) cooled to –78 °C with a dry ice/acetone bath was added a solution of DMSO (268 mg, 3.42 mmol) in CH_2Cl_2 (10 mL) slowly over 15 minutes. After stirring for 10 minutes, a solution of Example **71** (622 mg, 1.71 mmol) in CH_2Cl_2 (5 mL) was slowly added to the reaction mixture. The reaction was monitored for completion by thin layer chromatography and LC/MS. The solution became cloudy upon completion and the reaction was quenched at –78 °C by adding triethylamine (693 mg, 6.85 mmol). The solution became clear and was then warmed to room temperature. The reaction mixture was diluted with more CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by flash column chromatography (gradient, EtOAc/MeOH, 10:1 to 3:1) gave 185 mg (19% yield) of Example **86** which was used immediately upon isolation.

Example 87



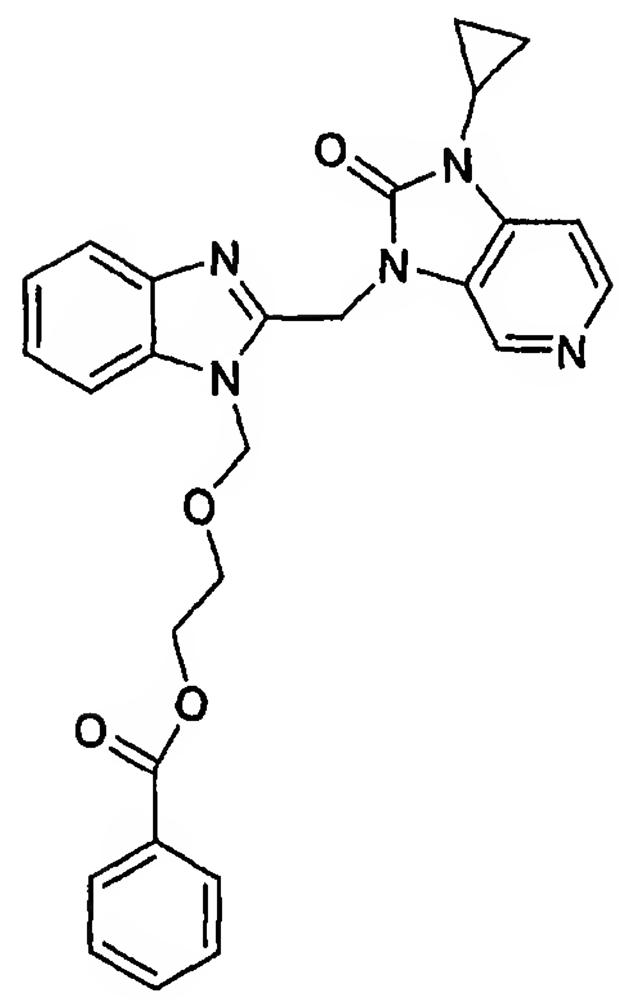
Example **87** was prepared according to the procedure described in *J. Med. Chem.*, **1996,** *39*, 2411-2421 by Yu, K.-L. et al. using aldehyde **86**:

A fresh solution of anhydrous 1M tetrabutylammonium fluoride in THF was prepared according to the procedure described by Cox et al in *J. Organic Chemistry*, **1984**, *49*, 3219-3220.

To a solution of Example **86** (150 mg, 0.42 mmol) in THF (10 mL) was added trimethyl(trifluoromethyl) silane (0.5M in THF, 1.25 mL, 0.62 mmol) followed by a catalytic amount of tetrabutylammonium fluoride (TBAF, 1M in THF, 8 μL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 hours and then warmed to room temperature. Additional trimethyl(trifluoromethyl) silane (0.5M in THF, 1.05 mL, 0.53 mmol) and TBAF (1M in THF, 8 μL) were added to push the reaction toward completion. The reaction was quenched with excess TBAF (1M in THF, 2.88 mL, 2.88 mmol) and the reaction mixture was allowed to stir for 18 hours. The solvent was evaporated and the residue was purified by flash column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 5:1) to give 106 mg (59% yield) of Example **87**.

^{1}H NMR (CD_3OD) δ 0.98-1.07 (m, 2 H), 1.08-1.16 (m, 1 H), 1.89-1.97 (m, 1 H), 2.08-2.14 (m, 1 H), 2.99-3.04 (m, 2 H), 3.91-3.95 (m, 1 H), 4.53-4.63 (m, 2 H), 5.46-5.55 (m, 2 H), 7.25-7.28 (m, 1 H), 7.33 (dt, J = 0.9, 7.8 Hz, 1 H), 7.40 (d, J = 5.5 Hz, 1 H), 7.58 (d, J = 8.1 Hz, 2 H), 8.26 (d, J = 5.4 Hz, 1 H), 8.30 (s, 1 H);
IR (KBr, cm^{-1}) 3422, 1723, 1613, 1504, 1412, 1173, 1131, 745;
MS m/e 432 (MH^+).

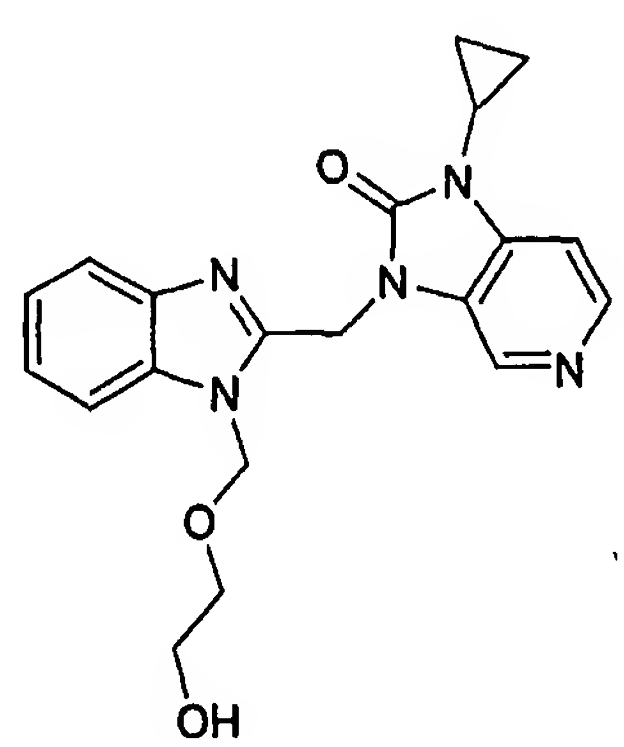
Example 88



^{1}H NMR ($CDCl_3$) δ 0.92-0.95 (m, 2 H), 1.03-1.07 (m, 2 H), 2.81-2.85 (m, 1 H), 3.53 (t, J = 4.8 Hz, 2 H), 4.07 (t, J = 4.8 Hz, 2 H), 5.36 (s, 2 H), 5.69 (s, 2 H), 7.04 (d, J = 5.5 Hz, 1 H), 7.19-7.23 (m, 3 H), 7.33-7.39 (m, 3 H), 7.48-7.51 (m, 1 H), 7.70-7.72 (m, 1 H), 7.86 (d, J = 8.3 Hz, 1 H), 8.22 (d, J = 5.2 Hz, 1 H), 8.52 (s, 1 H);

MS m/e 484 (MH^+).

Example 89

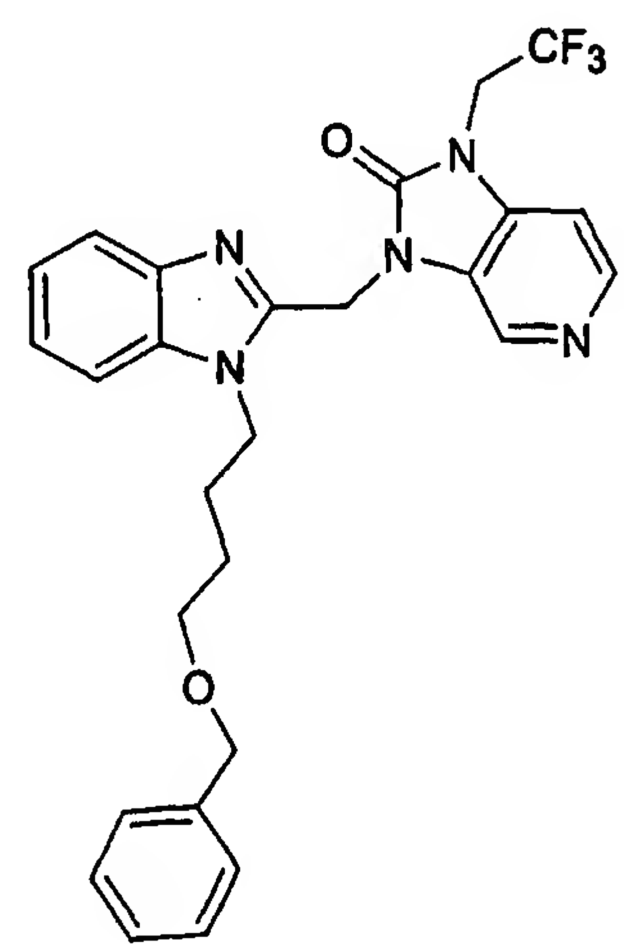


To a solution of Example **88** (30.5 mg, 0.06 mmol) in MeOH (1 mL) was added ammonia (2 M in MeOH, 1 mL). The reaction mixture was stirred at room

temperature for 16 hours. The solvent was concentrated. Purification by preparative HPLC (gradient, 10% MeOH in H_2O with 0.1% TFA to 90% MeOH in H_2O with 0.1% TFA) followed by treatment with excess 4 N HCl in dioxane gave Example **89** as the HCl salt.

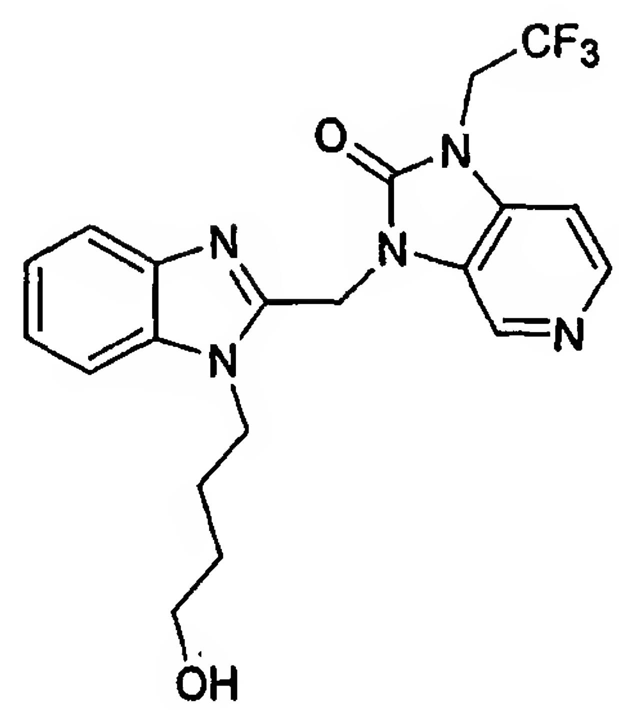
^{1}H NMR (CD_3OD) δ 1.11-1.17 (m, 2 H), 1.21-1.26 (m, 2 H), 3.13-3.20 (m, 1 H), 3.59-3.66 (m, 2 H), 3.72-3.77 (m, 2 H), 5.98 (s, 2 H), 6.11 (s, 2 H), 7.62 (t, J = 7.4 Hz, 1 H), 7.66 (t, J = 7.6 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.92 (d, J = 4.2 Hz, 1 h), 8.04 (d, J = 8.0 Hz, 1 H), 8.58 (d, J = 3.9 Hz, 1 H), 8.89 (s, 1 H);
MS m/e 380 (MH^+).

Example 90



MS m/e 510 (MH^+).

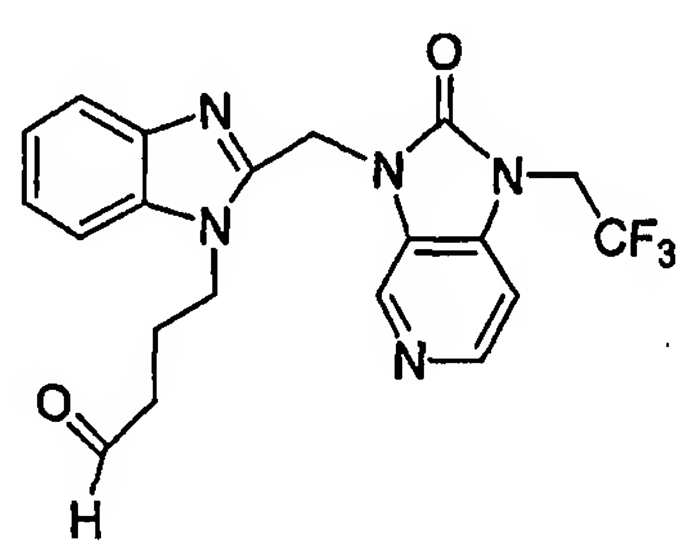
Example 91



Example **91** was prepared from Example **90** according to the same procedure described for Example **71**.

^{1}H NMR (DMSO-d_6) δ 1.53-1.59 (m, 2 H), 1.87-1.92 (m, 2 H), 3.47 (t, J = 6.4 Hz, 2 H), 4.54 (t, J = 7.6 Hz, 2 H), 5.17 (q, J = 9.0 Hz, 2 H), 5.89 (s, 2 H), 7.44 (t, J = 7.6 Hz, 1 H), 7.51 (t, J = 7.6 Hz, 1 H), 7.70 (d, J = 8.1 Hz, 1 H), 7.91 (d, J = 8.2 Hz, 1 H), 8.10 (d, J = 6.4 Hz, 1 H), 8.80 (d, J = 6.5 Hz, 1 H), 9.11 (s, 1 H).
MS m/e 420 (MH^+).

Example 92

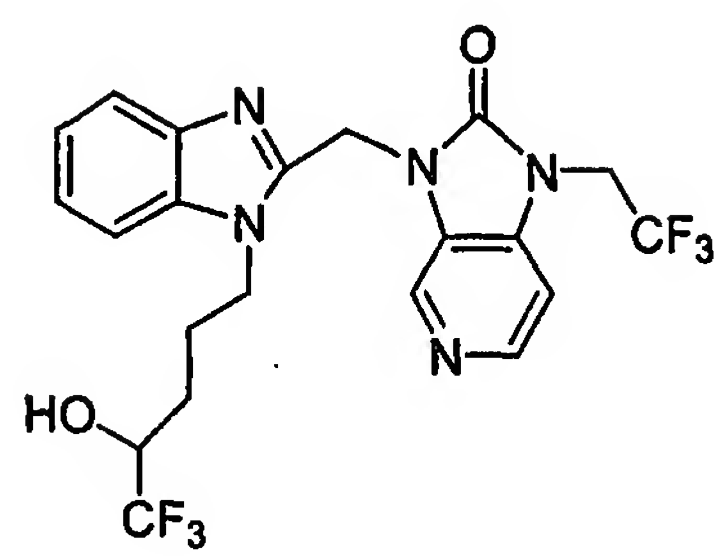


Example **92** was prepared from Example **91** according to the same procedure described for Example **86**.

^{1}H NMR ($CDCl_3$) δ 1.94-1.99 (m, 2 H), 2.59 (t, J = 6.7 Hz, 2 H), 4.31-4.35 (m, 2 H), 4.53 (q, J = 8.5 Hz, 2 H), 5.46 (s, 2 H), 7.07 (d, J = 6.4 Hz, 1 H), 7.27-7.34 (m,

2 H), 7.44 (d, J = 7.5 Hz, 1 H), 8.78 (dd, J = 0.9, 7.2 Hz, 1 H), 8.39 (d, J = 5.4 Hz, 1 H), 8.85 (s, 1 H), 9.78 (s, 1 H);
MS m/e 418 (MH^+).

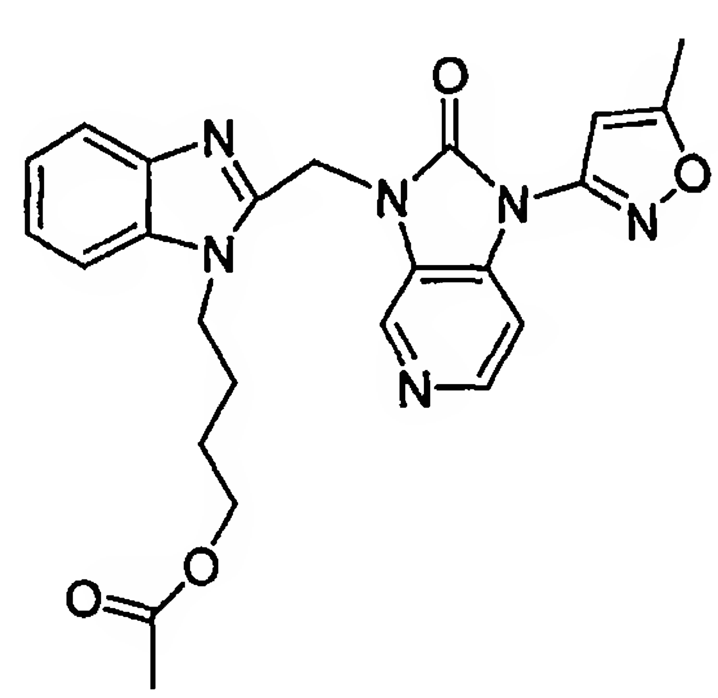
Example 93



Example **93** was prepared from Example **92** according to the same procedure described for Example **87**.

^{1}H NMR (CD_3OD) δ 1.60-1.73 (m, 1 H), 1.78-1.90 (m, 1 H), 2.00-2.14 (m, 2 H), 3.96-4.01 (m, 1 H), 4.53 (t, J = 7.8 Hz, 2 H), 4.94 (q, J = 8.9 Hz, 2 H), 5.69 (s, 2 H), 7.34-7.44 (m, 2 H), 7.60 (d, J = 7.8 Hz, 1 H), 7.68 (d, J = 7.5 Hz, 1 H), 7.92 (d, J = 6.3 Hz, 1 H), 8.60 (d, J = 5.7 Hz, 1 H), 8.82 (s, 1 H);
MS m/e 488 (MH^+).

Example 94



^{1}H NMR ($CDCl_3$) δ 1.68-1.73 (m, 2 H), 1.74-1.80 (m, 2 H), 1.99 (s, 3 H), 2.54 (s, 3 H), 4.04 (t, J = 6.3 Hz, 2 H), 4.35 (t, J = 7.5 Hz, 2 H), 5.48 (s, 2 H), 6.97 (s, 1 H), 7.27-7.35 (m, 3 H), 7.78-7.80 (m, 1 H), 8.00 (d, J = 5.4 Hz, 1 H), 8.46 (d, J = 5.4 Hz, 1 H), 8.86 (s, 1 H);

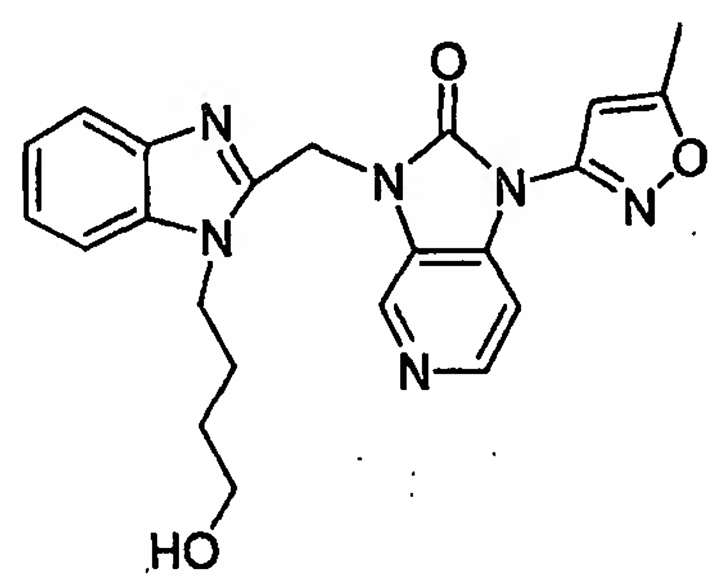
IR (KBr, cm^{-1}) 3421, 1727, 1599, 1527, 1484, 1457, 1257, 751;

MS m/e 461 (MH^+);

Anal. Calcd for $C_{24}H_{24}N_6O_4 \bullet 2.0\ H_2O$: C, 58.06; H, 5.68; N, 16.93

Found: C, 58.36; H, 5.55; N, 16.97.

Example 95



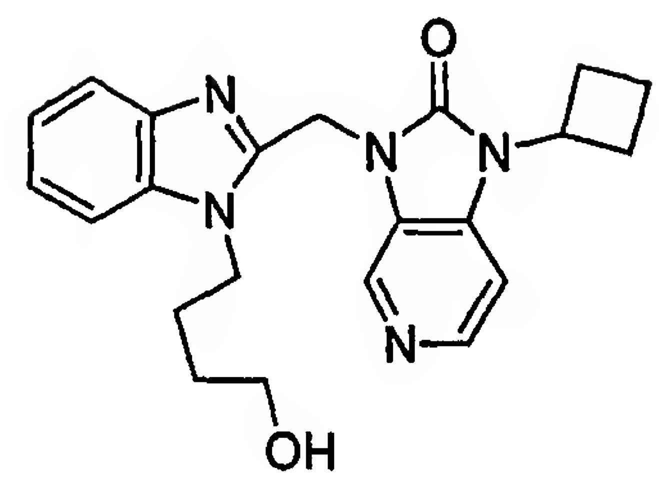
Example **95** was prepared from Example **94** according to the same procedure described for Example **73**.

^{1}H NMR ($CDCl_3$) δ 1.60-1.66 (m, 2 H), 1.79-1.85 (m, 2 H), 3.65 (t, J = 6.1 Hz, 2 H), 4.35 (t, J = 7.9 Hz, 2 H), 5.50 (s, 2 H), 6.95 (s, 1 H), 7.28-7.36 (m, 3 H), 7.77-7.79 (m, 1 H), 8.00 (d, J = 5.4 Hz, 1 H), 8.45 (d, J = 5.4 Hz, 1 H), 8.87 (s, 1 H);

IR (KBr, cm^{-1}) 3309, 1728, 1602, 1528, 1483, 1452, 1385, 1171, 827, 739;

MS m/e 419 (MH^+).

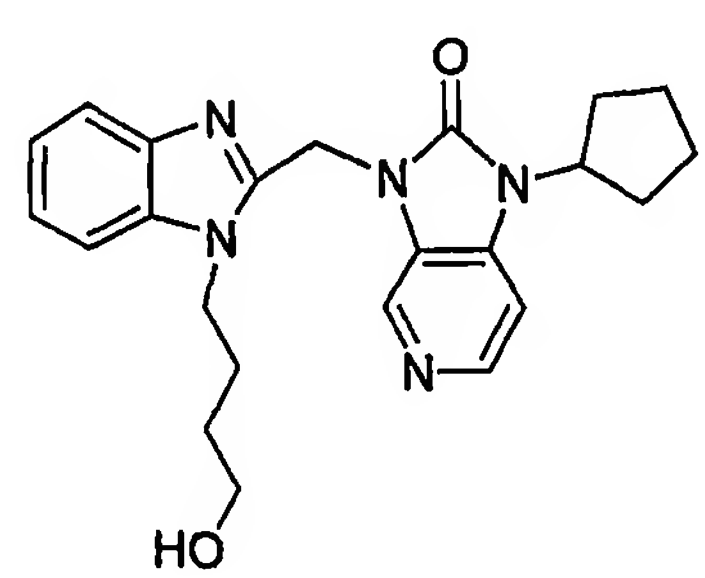
Example 96



Example **96** was prepared via synthesis of the acetate intermediate according to the same procedure described for Example **72** followed immediately by deprotection of the alcohol according to the same procedure described for Example **73**.

^{1}H NMR ($CDCl_3$) δ 1.61-1.67 (m, 2 H), 1.79-1.85 (m, 2 H), 1.90-2.05 (m, 2 H), 2.43-2.49 (m, 2 H), 2.81-2.89 (m, 2 H), 3.68 (t, J=6.0 Hz, 2 H), 4.34 (t, J=7.8 Hz, 2 H), 4.85-4.92 (m, 1 H), 5.43 (s, 2 H), 7.22-7.35 (m, 4 H), 7.75-7.77 (m, 1 H), 8.33 (d, J= 5.5 Hz, 1 H), 8.82 (s, 1 H);
MS m/e 392 (MH^+);
Anal. Calcd for $C_{22}H_{25}N_5O_2$• 0.5 H_2O: C, 65.98; H, 6.54; N, 17.49
Found: C, 65.71; H, 6.62; N, 17.37.

Example 97



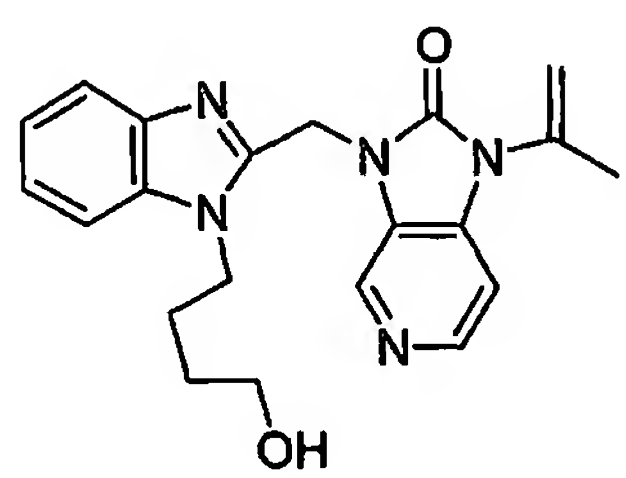
Example **97** was prepared via synthesis of the acetate intermediate according to the same procedure described for Example **72** followed immediately

by deprotection of the alcohol according to the same procedure described for Example **73**.

^{1}H NMR ($CDCl_3$) δ 1.61-1.67 (m, 2 H), 1.75-1.83 (m, 4 H), 1.95-2.02 (m, 2 H), 2.05-2.11 (m, 4 H), 3.68 (t, J = 6.0 Hz, 2 H), 4.35 (t, J = 7.9 Hz, 2 H), 4.82-4.89 (m, 1 H), 5.43 (s, 2 H), 7.04 (d, J = 5.5 Hz, 1 H), 7.22-7.30 (m, 2 H), 7.32-7.35 (m, 1 H), 7.76-7.78 (m, 1 H), 8.30 (d, J = 5.5 Hz, 1 H), 8.82 (s, 1 H);
IR (KBr, cm^{-1}) 3272, 2945, 2870, 1710, 1607, 1496, 1395, 742;
MS m/e 406 (MH^+);

Anal. Calcd for $C_{23}H_{28}N_5O_2$:		C, 67.95; H, 6.94; N, 17.22
	Found:	C, 67.78; H, 6.72; N, 16.92.

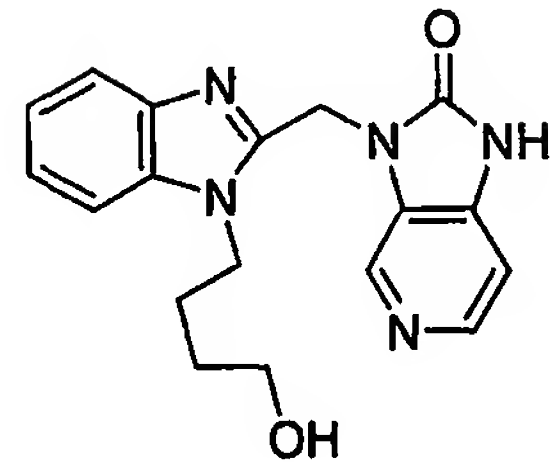
Example 98



Example **98** was prepared via synthesis of the acetate intermediate according to the same procedure described for Example **72** followed immediately by deprotection of the alcohol according to the same procedure described for Example **73**.

^{1}H NMR (DMSO-d_6) δ 1.43-1.48 (m, 2 H), 1.66-1.69 (m, 2 H), 2.18 (s, 3 H), 3.37-3.41 (m, 2 H), 4.35 (t, J = 7.3 Hz, 2 H), 4.47 (t, J = 5.1 Hz, 1 H), 5.25 (s, 1 H), 5.44 (s, 2 H), 5.46 (d, J = 1.0 Hz, 1 H), 7.17-7.27 (m, 3 H), 7.57-7.60 (m, 2 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.48 (s, 1 H);
MS m/e 378 (MH^+).

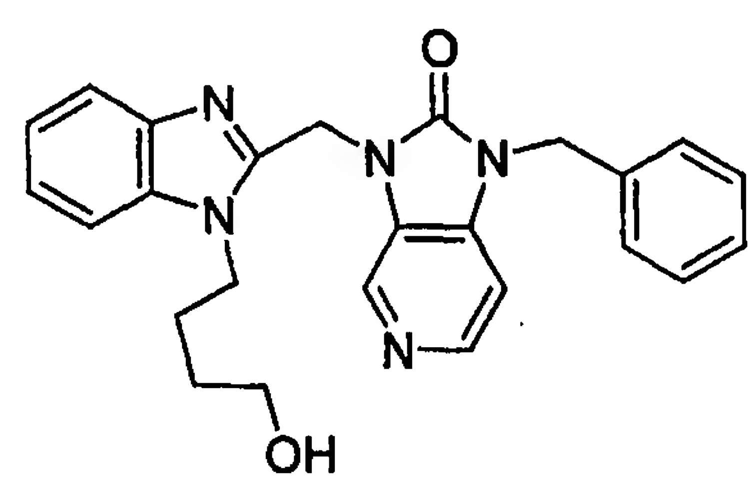
Example 99



Example **99** was prepared from Example **98** according to the same procedure described for Example **17**.

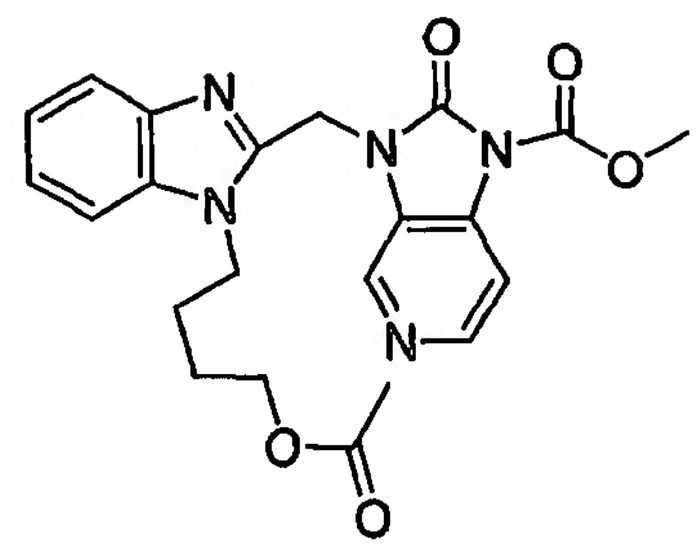
^{1}H NMR (DMSO-d_6) δ 1.44-1.48 (m, 2 H), 1.65-1.68 (m, 2 H), 3.38-3.42 (m, 2 H), 4.34 (t, J = 7.5 Hz, 2 H), 4.47 (t, J = 5.1 Hz, 1H), 5.38 (s, 1 H), 7.07 (d, J = 5.2 Hz, 1 H), 7.19 (t, J = 7.0 Hz, 1 H), 7.23 (t, J = 7.0 Hz, 1 H), 7.57 (t, J = 8.0 Hz, 1 H), 8.15 (d, J = 5.1 Hz, 1 H), 8.34 (s, 1 H), 11.59 (s, 1 H);
MS m/e 338 (MH^+).

Example 100



^{1}H NMR (CD_3OD) δ 1.54-1.60 (m, 2 H), 1.86-1.92 (m, 2 H), 3.52 (t, J = 6.2 Hz, 2 H), 4.45 (t, J = 7.7 Hz, 2 H), 5.20 (s, 1 H), 5.65 (d, J = 6.8 Hz, 2 H), 7.21-7.32 (m, 4 H), 7.34-7.37 (m, 3 H), 7.52-7.55 (m, 1 H), 7.63 (t, J = 8.4 Hz, 1 H), 8.37 (d, J = 6.5 Hz, 1 H), 8.68 (s, 1 H);
MS m/e 428 (MH^+).

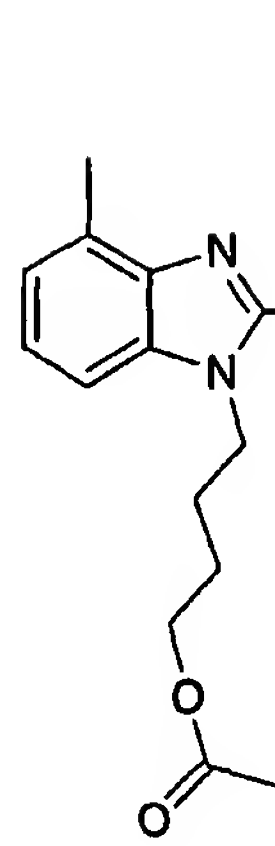
Example 101



To a solution of Example **99** (34 mg, 0.1 mmol) and 4-dimethylaminopyridine (DMAP, 2.0 mg, 0.02 mmol) in pyridine (1 ml) was added acetic anhydride (22 mg, 0.22 mmol) at room temperature. After stirring for 12 hours, the reaction mixture was diluted with EtOAc (10 ml) and washed twice with H_2O and brine. The combined organic extracts were dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatagraphy (CH_2Cl_2/MeOH, 20:1) to yield 35 mg (82%yield) of Example **101** as a white solid.

^{1}H NMR ($CDCl_3$) δ 1.69-1.82 (m, 4 H), 2.00 (s, 3 H), 2.80 (s, 3 H), 4.06 (t, J = 6.2 Hz, 2 H), 4.34 (t, J = 6.6 Hz, 2 H), 5.39 (s, 2 H), 7.26-7.32 (m, 3 H), 7.75-7.78 (m, 1 H), 8.03 (d, J = 5.1 Hz, 1 H), 8.42 (d, J = 3.2 Hz, 1 H), 8.82 (s, 1 H);
MS m/e 422 (MH^+).

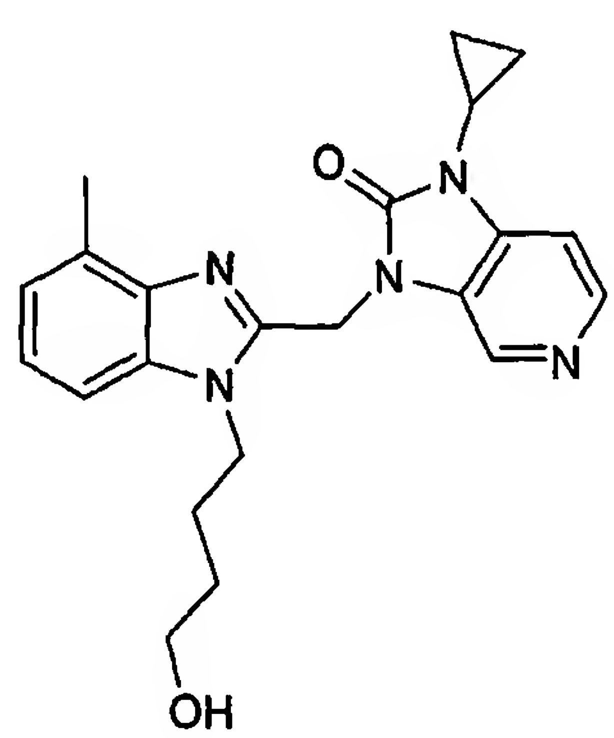
Example 102



^{1}H NMR (DMSO-d_6) δ 0.64-0.68 (m, 2 H), 0.81-0.86 (m, 2 H), 1.28-1.37 (m, 4 H), 1.72 (s, 3 H), 2.27 (s, 3 H), 2.73-2.77 (m, 1 H), 3.72 (t, J = 6.2 Hz, 2 H), 4.07 (t, J = 7.1 Hz, 2 H), 5.14 (s, 2 H), 6.76 (d, J = 7.3 Hz, 1 H), 6.90 (t, J = 7.7 Hz, 1 H), 7.03 (d, J = 5.25 Hz, 1 H), 7.13 (d, J = 8.1 Hz, 1 H), 8.00 (d, J = 5.25 Hz, 1 H), 8.23 (s, 1 H);

MS m/e 434 (MH^+).

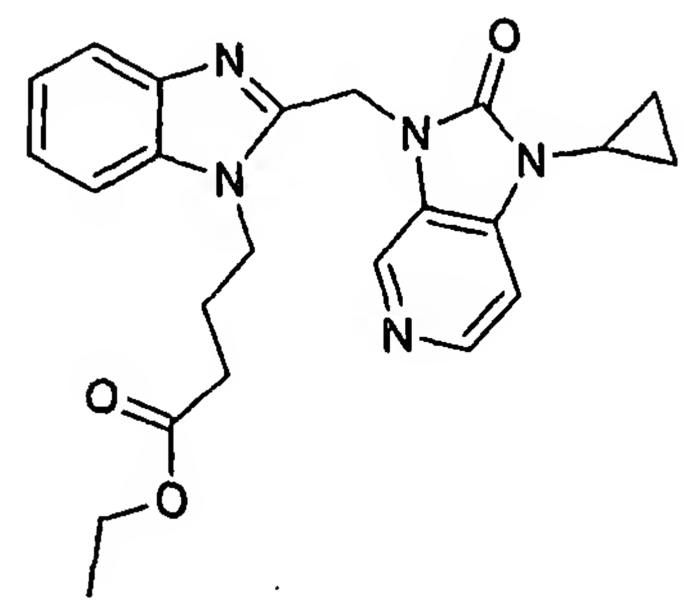
Example 103



Example **103** was prepared from Example **102** according to the same procedure described for Example **73**.

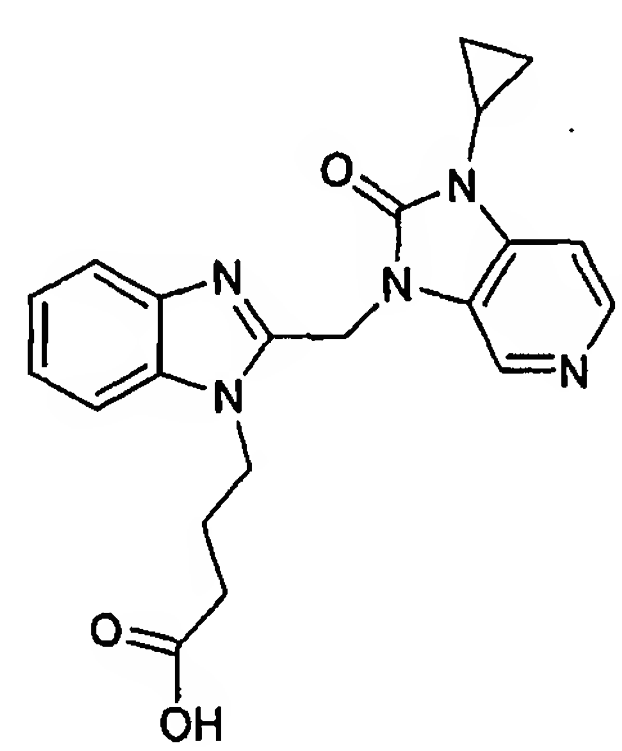
^{1}H NMR (DMSO-d_6) δ 0.90-0.95 (m, 2 H), 1.05-1.10 (m, 2 H), 1.35-1.41 (m, 2 H), 1.50-1.55 (m, 2 H), 2.51 (s, 3 H), 2.97-3.00 (m, 1 H), 4.27 (t, J = 7.5 Hz, 2 H), 4.43 (t, J = 5.0 Hz, 2 H), 5.38 (s, 2 H), 7.00 (d, J = 7.2 Hz, 1 H), 7.13 (t, J = 7.7 Hz, 1 H), 7.27 (d, J = 5.2 Hz, 1 H), 7.34 (d, J = 8.1 Hz, 1 H), 8.23 (d, J = 5.2 Hz, 1 H), 8.45 (s, 1 H);
MS m/e 392 (MH^+).

Example 104



^{1}H NMR ($CDCl_3$) δ 1.00-1.02 (m, 2 H), 1.14-1.18 (m, 2 H), 1.22 (t, J = 7.1 Hz, 3 H), 2.38 (t, J = 7.15 Hz, 2 H), 2.91-2.96 (m, 1 H), 4.10 (q, J = 7.2 Hz, 2 H), 4.38 (t, J = 7.6 Hz, 2 H), 5.37 (s, 2 H), 7.16 (d, J = 5.4 Hz, 1 H), 7.24-7.30 (m, 4 H), 7.39 (d, J = 6.6 Hz, 1 H), 7.75 (d, J = 7.0 Hz, 1 H), 8.33 (d, J = 5.3 Hz, 1 H), 8.71 (s, 1 H);
MS m/e 419 (MH^+).

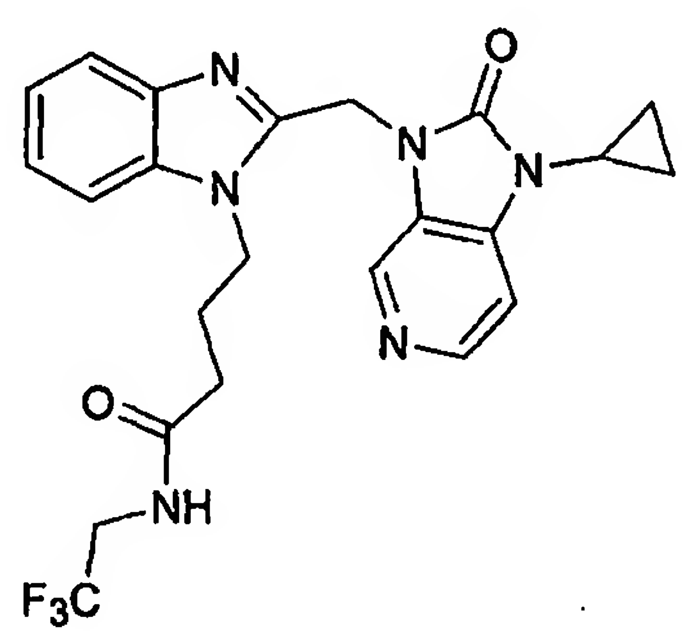
Example 105



A mixture of Example **104** (346 mg, 0.83 mmol) and aqueous sodium hydroxide (1N, 4.1 mL, 4.13 mmol) were stirred in MeOH (5 mL) for 14 hours at room temperature. The mixture was neutralized with HCl followed by flash column chromatography to give Example **105**.

^{1}H NMR ($CDCl_3$) δ 1.13-1.16 (m, 2 H), 1.22-1.25 (m, 2 H), 2.36-2.41 (m, 4 H), 3.09-3.12 (m, 1 H), 4.56 (t, J = 6.6 Hz, 2 H), 5.91 (s, 2 H), 7.47-7.57 (m, 4 H), 7.93 (d, J = 7.6 Hz, 1 H), 8.37 (d, J = 6.4 Hz, 1 H), 9.17 (s, 1 H);
MS m/e 392 (MH^+).

Example 106

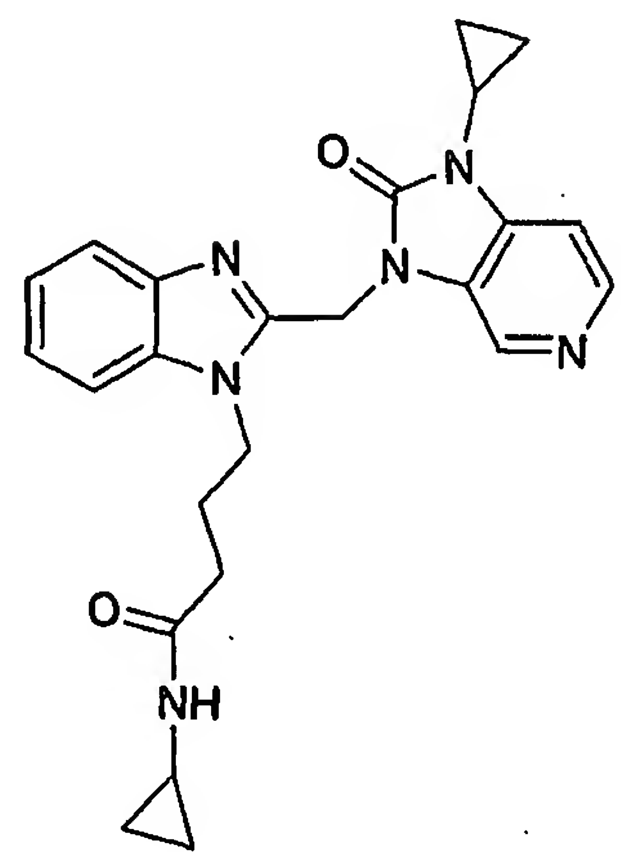


A solution of Example **105** (0.23 g, 0.50 mmol), 1-hydroxybenzotriazole hydrate (HOBT, 75 mg, 0.54 mmol), trifluoroethylamine hydrocloride (75 mg, 0.54 mmol), and N-methylmorpholine (0.21 g, 2.16 mmol) was stirred at room temperature for 30 minutes until a homogeneous solution resulted. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDAC ,103 mg, 0.54 mmol) was added and the mixture was stirred for 12 hours. The solution was concentrated and the residue dissolved in EtOAc and washed with water and saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to give 35 mg (18% yield) of Example **106** as a white solid.

^{1}H NMR (DMSO-d_6) δ 0.89-0.93 (m, 2 H), 1.06-1.08 (m, 2 H), 1.86-1.89 (m, 2 H), 2.27-2.30 (m, 2 H), 2.98-3.00 (m, 1 H), 4.31-4.34 (m, 2 H), 5.40 (s, 2 H),

7.18-7.23 (m, 1 H), 7.25-7.29 (m, 2 H), 7.57-7.58 (m, 2 H) 8.25-8.26 (m, 1 H) 8.41 (s, 1 H), 8.57-8.60 (m, 1 H);
MS m/e 472 (MH^+).

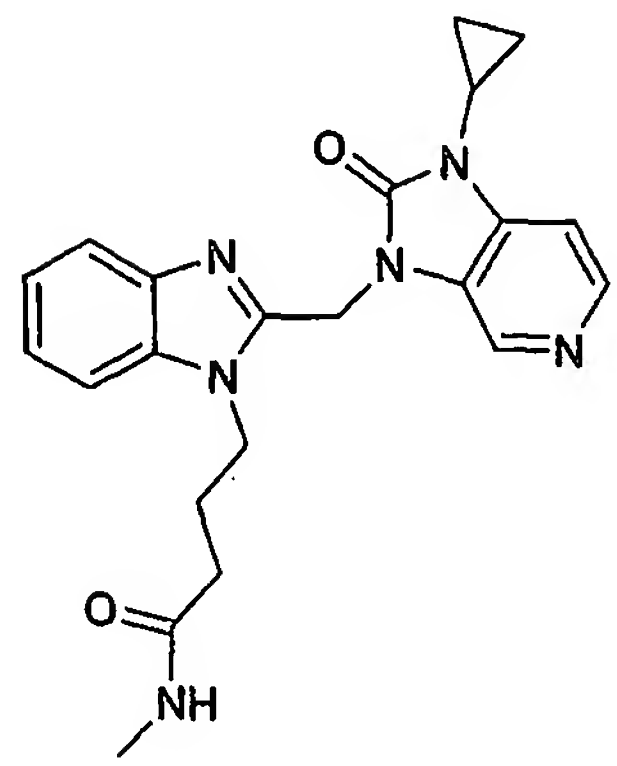
Example 107



Example **104** (100 mg, 0.24 mmol) in neat cyclopropylamine (1.22 g, 21.40 mmol) was heated at 105 °C in a sealed tube for 18 hours. The reaction mixture was concentrated and the residue was purified by flash column chromatography to give Example **107**.

^{1}H NMR ($CDCl_3$) δ 0.45-0.48 (m, 2 H), 0.74-0.78 (m, 2 H), 0.98-1.03 (m, 2 H), 1.14-1.18 (m, 2 H), 1.99-2.04 (m, 2 H), 2.20 (t, J = 6.9 Hz, 2 H), 2.67-2.70 (m, 1 H), 2.92-2.96 (m, 1 H), 4.37 (t, J = 7.6 Hz, 2 H), 5.36 (s, 2 H), 7.14 (d, J = 5.2 Hz, 1 H0, 7.24-7.29 (m, 2 H), 7.44 (d, J = 7.0 Hz, 1 H), 7.75 (d, J = 7.4 Hz, 1 H), 8.34 (d, J = 5.2 Hz, 1 H), 8.70 (s, 1 H);
MS m/e 431 (MH^+).

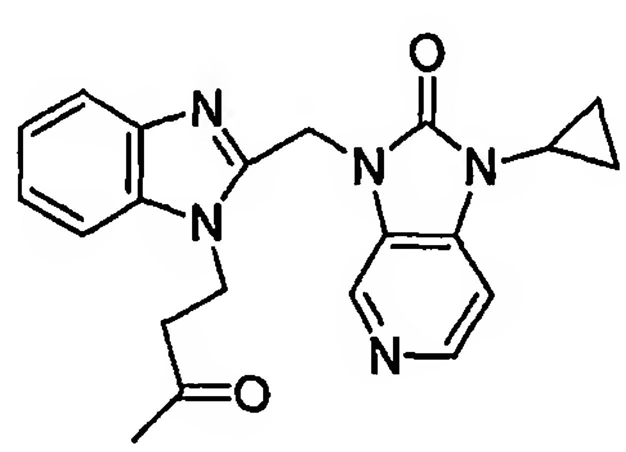
Example 108



Example **104** (52 mg, 0.12 mmol) in methylamine (40% aqueous solution, 4 mL) was heated at 120 °C in a sealed tube for 18 hours. The solvent was evaporated and the residue purified by flash column chromatography to give Example **108** as a 2:1 mixture of cis/trans rotomers.

^{1}H NMR ($CDCl_3$) δ 0.96-1.00 (m, 2 H), 1.08-1.14 (m, 2 H), 1.94-2.02 (m, 2 H), 2.19-2.23 (m, 2 H), 2.75 (d, J = 6.0 Hz, 3 H), 2.88-2.92 (m, 1 H), 4.29-4.36 (m, 2 H), 5.33, 5.34 (s, 2 H), 7.07, 7.10 (d, J = 6.5 Hz, 1 H), 7.11-7.27 (m, 2 H), 7.66-7.71 (m, 1 H), 8.25, 8.28 (d, J = 6.7 Hz, 1 H), 8.57, 8.63 (s, 1 H);
MS m/e 405 (MH^+).

Example 109

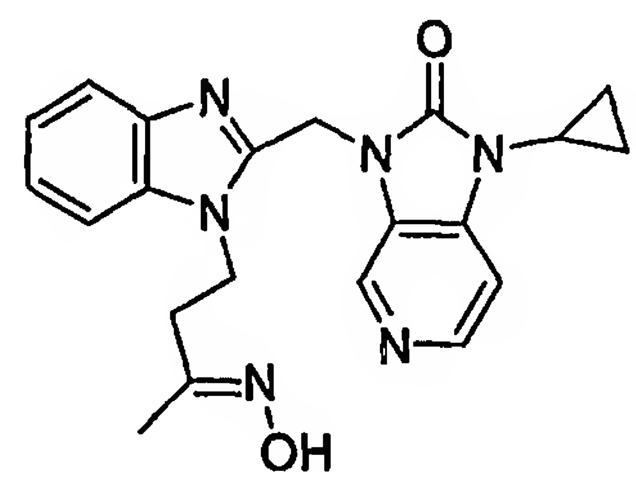


A mixture of Example **47** (500 mg, 1.64 mmol) and methyl vinyl ketone (574 mg, 8.2 mmol) in EtOH (10 ml) was heated to reflux for 8 hours. After

cooling, the solid was collected by filtration to give 378 mg (61%) of Example **109** as a white solid.

^{1}H NMR ($CDCl_3$) δ 1.01-1.05 (m, 2 H), 1.15-1.19 (m, 2 H), 2.10 (s, 3 H), 2.91-2.96 (m, 3 H), 4.60 (t, J=6.4 Hz, 2 H), 5.53 (s, 2 H), 7.17 (d, J=5.4 Hz, 1 H), 7.24-7.30 (m, 2 H), 7.32-7.34 (m, 1 H), 7.73-7.75 (m, 1 H), 8.34 (d, J=5.4 Hz, 1 H), 8.69 (s, 1 H);
MS m/e 376 (MH^+).

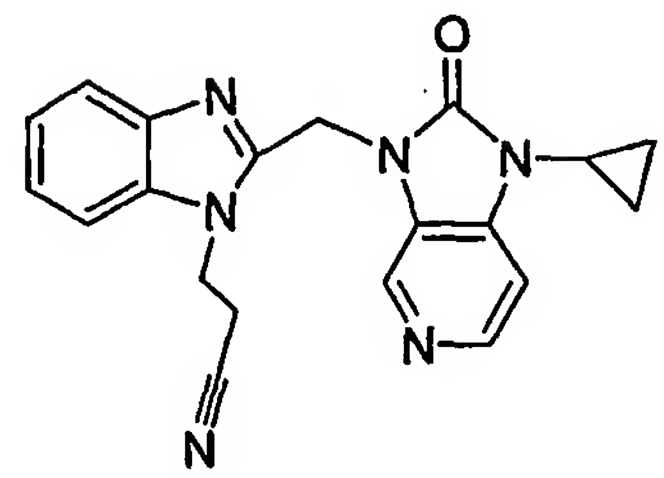
Example 110



A mixture of Example **109** (37 mg, 0.10 mmol) and hydroxylamine hydrochloride (7.6 mg, 0.11 mmol) in MeOH (2 ml) was heated to reflux for 2 hours, diluted with EtOAc (20 ml) and washed with aqueous saturated $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, and evaporated to give 34 mg (87% yield) of Example **110** as white solid.

^{1}H NMR ($CDCl_3$) δ 1.01-1.05 (m, 2 H), 1.15-1.19 (m, 2 H), 1.89 (s, 3 H), 2.64 (t, J=6.5 Hz, 2 H), 2.89-2.92 (m, 1 H), 4.58 (t, J=6.6 Hz, 2 H), 5.41 (s, 2 H), 7.12-7.31 (m, 4 H), 7.69-7.72 (m, 1 H), 8.29 (d, J= 4.8 Hz, 1 H), 8.57 (s, 1 H);
MS m/e 391 (MH^+).

Example 111



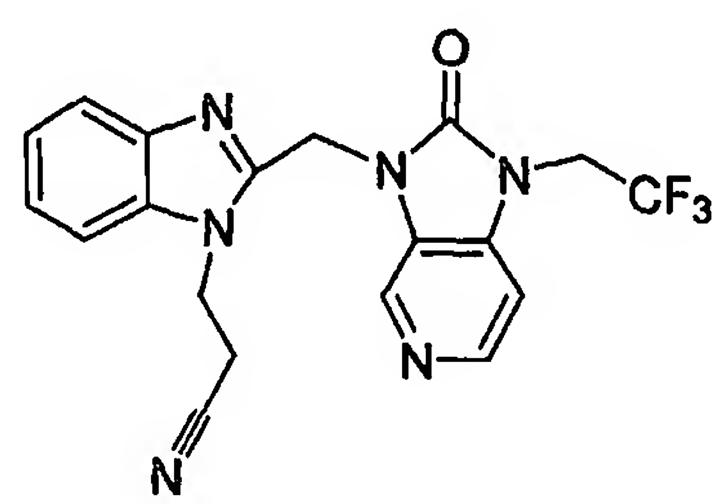
^{1}H NMR ($CDCl_3$) δ 1.03-1.07 (m, 2 H), 1.16-1.20 (m, 2 H), 2.86 (t, J = 6.5 Hz, 2 H), 2.93-2.97 (m, 1 H), 4.78 (t, J = 6.5 Hz, 2 H), 5.43 (s, 2 H), 7.18 (d, J = 5.4 Hz, 1 H), 7.30-7.36 (m, 3 H), 7.81-7.82 (m, 1 H), 8.36 (d, J = 5.4 Hz, 1 H), 8.84 (s, 1 H);

IR (KBr, cm^{-1}) 3405, 1709, 1605, 1500, 1466, 1455, 1411, 1179, 750;

MS m/e 359 (MH^+);

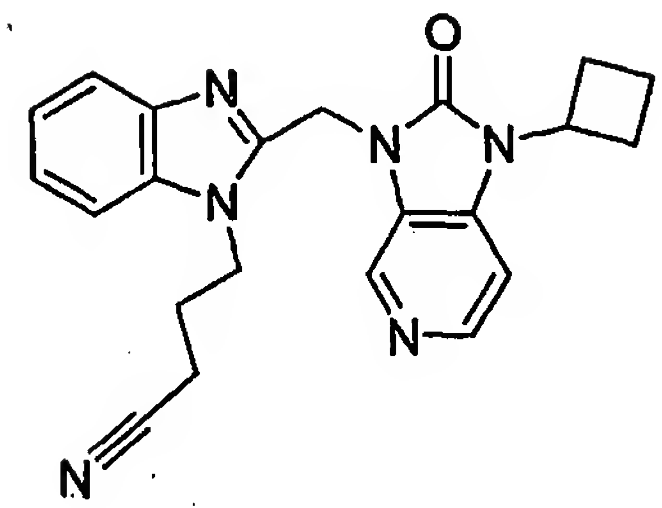
Anal. Calcd for $C_{20}H_{18}N_6O \bullet 0.5H_2O$:	C, 65.38; H, 5.21; N, 22.87
Found:	C, 65.49; H, 5.09; N, 22.41.

Example 112



^{1}H NMR (CD_3OD) δ 3.11 (t, J = 6.6 Hz, 2 H), 4.72-4.82 (m, 4 H), 5.59 (s, 2 H), 7.28-7.38 (m, 3 H), 7.60-7.64 (m, 2 H), 8.29 (d, J = 5.7 Hz, 1 H), 8.53 (s, 1 H).

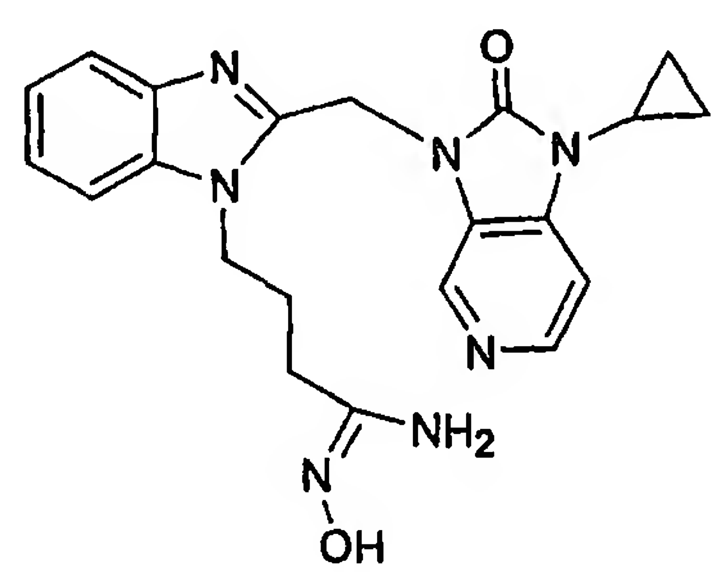
Example 113



^{1}H NMR ($CDCl_3$) δ 1.90-2.10 (m, 4 H), 2.43-2.49 (m, 4 H), 2.80-2.89 (m, 2 H), 4.48 (t, J=7.4 Hz, 2 H), 4.84-4.90 (m, 1 H), 5.40 (s, 2 H), 7.21-7.38 (m, 4 H), 7.77-7.79 (m, 1 H), 8.34 (d, J= 5.5 Hz, 1 H), 8.82 (s, 1 H);
MS m/e 387 (MH^+);

Anal. Calcd for $C_{22}H_{22}N_6O$:	C, 68.37; H, 5.73; N, 21.74
Found:	C, 68.21; H, 5.83; N, 21.71.

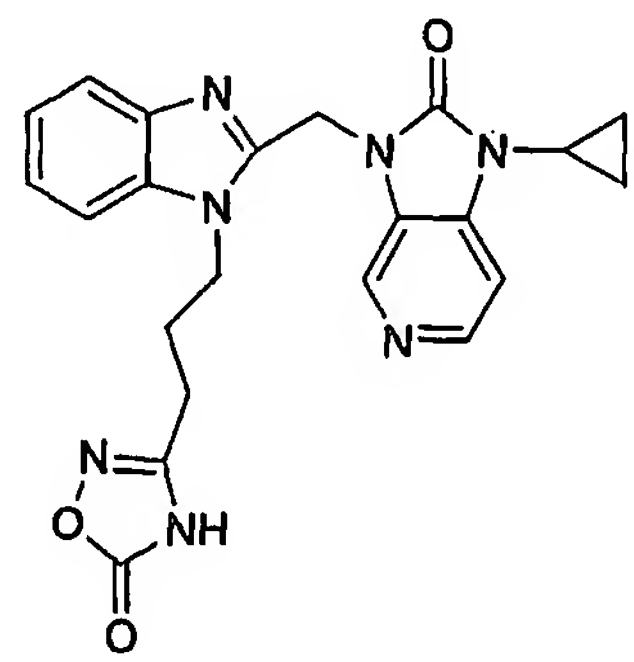
Example 114



A mixture of Example **26** (610 mg, 1.62 mmol), hydroxylamine hydrochloride (408 mg, 5.87 mmol) and potassium carbonate (450 mg, 3.24 mmol) were stirred in a EtOH and H_2O (2:1 ratio mixture, 60 mL) at 80 °C for 18 hours. The solvent was evaporated and the residue was diluted with H_2O to dissolve inorganic salts. The white solid was filtered and dried under high vacuum to give 545 mg (83% yield) of Example **114** as a white solid.

^{1}H NMR (DMSO-d_6) δ 0.90-0.93 (m, 2 H), 1.05-1.07 (m, 2 H), 1.87-1.90 (m, 2 H), 2.06 (t, J = 7.5 Hz, 2 H), 3.00-3.02 (m, 1 H), 4.32 (t, J = 7.6 Hz, 2 H), 5.41 (s, 2 H), 5.46 (bs, 2 H), 7.17 (t, J = 7.3 Hz, 1 H), 7.24 (t, J = 7.3 Hz, 1 H), 7.29 (d, J = 5.2 Hz, 1 H), 7.57 (d, J = 7.9 Hz, 1 H), 7.60 (d, J = 8.0 Hz, 1 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.40 (s, 1 H), 8.84 (s, 1 H).

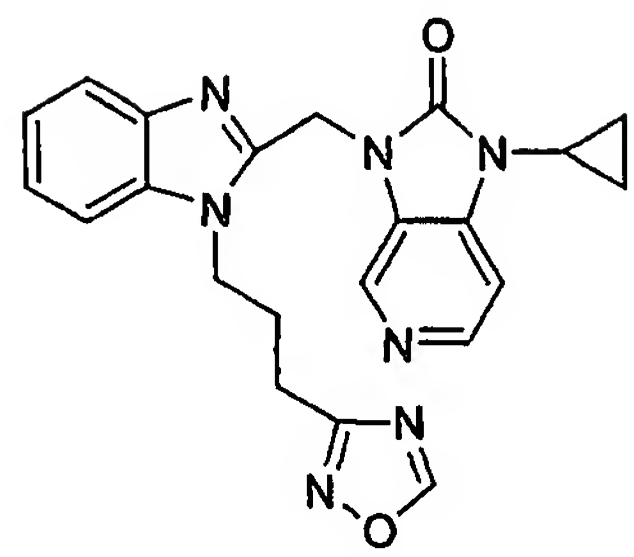
Example 115



Example **114** (210 mg, 0.52 mmol) was treated with phosgene (20% in toluene, 2.56 g, 5.2 mmol) and heated to reflux for 12 hours. Additional phosgene (20% in toluene 2.56 g, 5.2 mmol) was added and the mixture heated to reflux for another 6 hours. The solution was concentrated to half volume and the white solid was isolated by filtration to give 138 mg (62% yield) of Example **115**.

^{1}H NMR (DMSO-d_6) δ 1.05-1.05 (bs, 2 H), 1.15-1.16 (m, 2 H), 2.21-2.26 (m, 2 H), 2.71-2.75 (m, 2 H), 3.15-3.17 (m, 1 H), 4.51-4.58 (m, 2 H), 5.74-5.78 (m, 2 H), 7.37-7.40 (m, 1 H), 7.45-7.47 (m, 1 H), 7.63-7.66 (m, 1 H), 7.84-7.89 (m, 2 H), 8.64 (d, J = 6.4 Hz, 1 H), 8.92-8.95 (m, 1 H);
MS m/e 432 (MH$^+$).

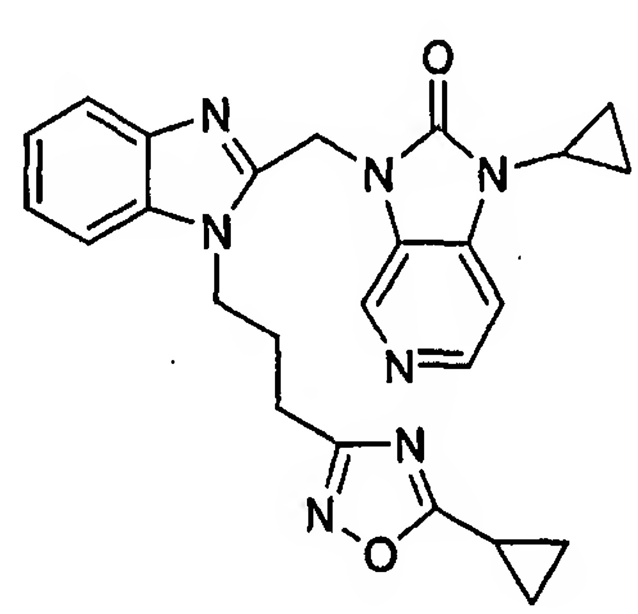
Example 116



A mixture of the Example **114** (100 mg, 0.24 mmol) was heated to reflux in triethylorthoformate (2.5 mL) for 12 hours. The solution was concentrated and the residue purified by preparative HPLC (C18, gradient 0-100% MeOH/H_2O with 0.1% trifluoroacetic acid). The product was treated with 4 N HCl in dioxane and concentrated to give 38 mg (35% yield) of the Example **116** as the hydrochloride salt.

^1H NMR (DMSO-d_6) δ 0.97-1.02 (m, 2 H), 1.10-1.16 (m, 2 H), 2.25-2.35 (m, 2 H), 2.95-2.99 (m, 2 H), 3.14-3.16 (m, 1 H), 4.55-4.65 (m, 2 H), 5.77 (s, 2 H), 7.39-7.41 (m, 1 H), 7.46-7.48 (m, 1 H), 7.66-7.68 (m, 1 H), 7.84-7.90 (m, 2 H), 8.64 (d, J = 6.1 Hz, 1 H), 8.94 (s, 1 H), 9.57 (s, 1 H);
MS m/e 416 (MH^+).

Example 117

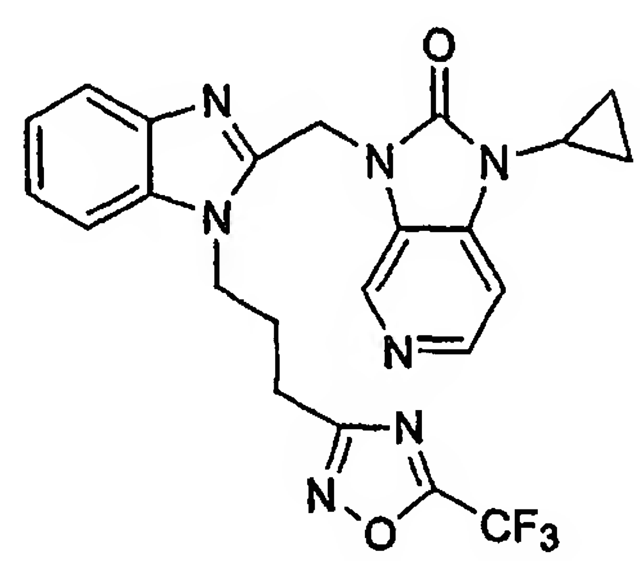


A mixture of Example **114** (250 mg, 0.62 mmol) was heated to reflux with cyclopropanecarbonyl chloride (354 mg, 3.39 mmol) and pyridine (2 mL) for 12

hours. The solution was concentrated and the residue purified by preparative HPLC (C18, gradient 0-100% $MeOH/H_2O$ with 0.1% trifluoroacetic acid). The product was treated with 4N HCl in dioxane and concentrated to give 80 mg (28% yield) of Example **117** as the hydrochloride salt.

^{1}H NMR (DMSO-d_6) δ 1.04-1.06 (m, 4H), 1.13-1.15 (m, 2 H), 1.20-1.23 (m, 2 H), 2.21-2.31 (m, 2 H), 2.83-2.85 (m, 2 H), .3.11-3.19 (m, 1 H), 3.65-3.75 (m, 1 H), 4.55-4.57 (m, 2 H), 5.75 (s, 2 H), 7.35-7.42 (m, 1 H), 7.45-7.52 (m, 1 H), 7.65 (d, J = 8.1 Hz , 1 H), 7.83-7.85 (m, 2 H), 8.62 (d, J = 8.1 Hz, 1 H), 8.92 (s, 1 H);
MS m/e 456 (MH^+).

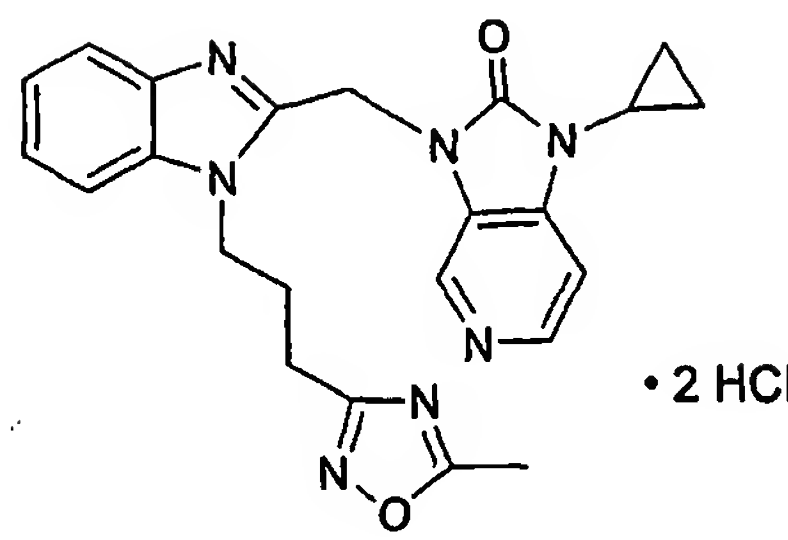
Example 118



Example **118** was prepared according to the same procedure described for Example **117** using trifluoroacetic anhydride.

^{1}H NMR (DMSO-d_6) δ 1.02-1.05 (m, 2 H), 1.12-1.16 (m, 2 H), 2.31-2.34 (m, 2 H), 3.10 (t, J = 7.3 Hz, 2 H), 3.13-3.16 (m, 1 H), 4.59 (t, J = 7.6 Hz, 2 H), 5.74 (s, 2 H), 7.38 (t, J = 7.8 Hz, 1 H), 7.45 (t, J = 7.4 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.85 (d, J = 7.7 Hz, 1 H), 7.88 (d, J = 8.2 Hz, 1 H), 8.63 (d, J = 8.2 Hz, 1 H), 8.94 (s, 1 H);
MS m/e 483 (MH^+).

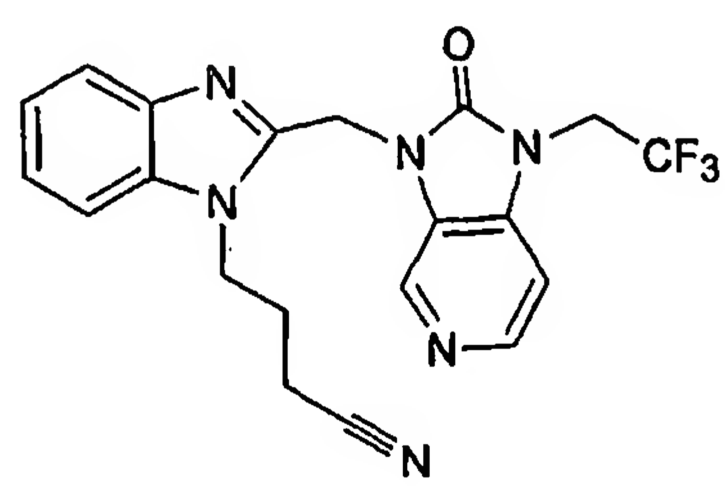
Example 119



Example **119** was prepared according to the same procedure described for Example **117** using acetic anhydride.

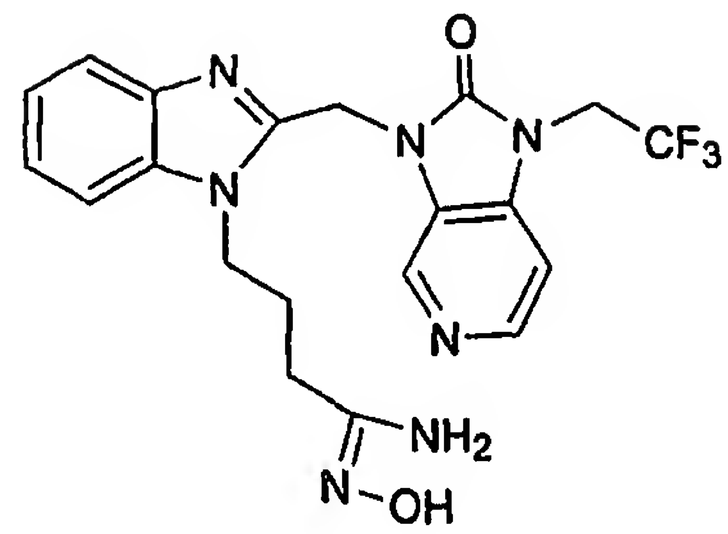
^{1}H NMR (DMSO-d_6) δ 1.01-1.05 (m, 2 H), 1.13-1.15 (m, 2 H), 2.24-2.28 (m, 2 H), 2.55 (s, 3 H), 2.85-2.88 (m, 1 H), 3.15-3.18 (m, 2 H), 4.55 (t, J = 7.4 Hz, 2 H), 5.71 (bs, 2 H), 7.29-7.38 (m, 1 H), 7.40-7.47 (m, 1 H), 7.64 (d, J = 7.4 Hz, 1 H), 7.80-7.86 (m, 2 H), 8.63 (d, J = 6.4 Hz, 1 H), 8.90 (s, 1 H);
MS m/e 430 (MH^+).

Example 120



^{1}H NMR (DMSO-d_6) δ 2.06-2.12 (m, 2 H), 2.63 (t, J = 7.3 Hz, 2 H), 4.42 (t, J = 7.5 Hz, 2 H), 4.92 (q, J = 9.3 Hz, 2 H), 5.51 (s, 2 H), 7.18 (t, J = 7.5 Hz, 1 H), 7.27 (t, J = 7.5 Hz, 1 H), 7.45 (d, J = 5.2 Hz, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.62 (d, J = 8.2 Hz, 1 H), 8.33 (d, J = 5.5 Hz, 1 H), 8.51 (s, 1 H).

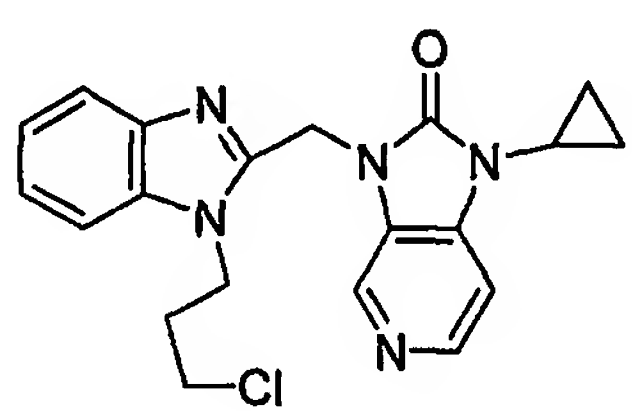
Example 121



Example **121** was prepared from Example **120** according to the same procedure as Example **114**.

^{1}H NMR (DMSO-d_6) δ 1.91-1.98 (m, 2 H), 2.30 (t, J = 7.0 Hz, 2 H), 4.37 (t, J = 7.7 Hz, 2 H), 4.91 (q, J = 9.1 Hz, 2 H), 5.51 (s, 2 H), 7.15-7.18 (m, 1 H), 7.23-7.27 (m, 1 H), 7.44 (d, J = 5.2 Hz, 1 H), 7.55 (d, J = 7.9 Hz, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 8.06 (bs, 1 H), 8.31 (d, J = 5.2 Hz, 2 H), 8.46 (s, 1 H), 9.48 (s, 1 H);
MS m/e 448 (MH^+).

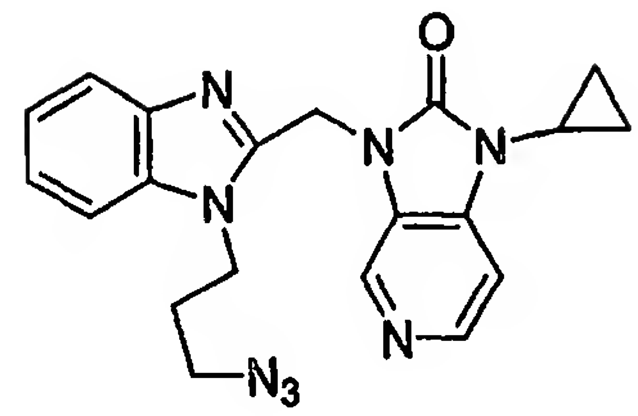
Example 122



^{1}H NMR ($CDCl_3$) δ 1.00-1.06 (m, 2 H), 1.15-1.19 (m, 2 H), 2.14-2.19 (m, 2 H), 2.91-2.95 (m, 1 H), 3.55 (t, J=6.0 Hz, 2 H), 4.52 (t, J=6.7 Hz, 2 H), 5.40 (s, 2 H), 7.14-7.15 (m, 1 H), 7.26-7.32 (m, 2 H), 7.39-7.40 (m, 1 H), 7.76-7.78 (m, 1 H), 8.34 (d, J=5.0 Hz, 1 H), 8.72 (s, 1 H);
MS m/e 382 (MH^+);

Anal. Calcd for $C_{20}H_{20}ClN_5O$:	C, 62.90; H, 5.27; N, 18.34
Found:	C, 62.58; H, 5.17; N, 18.18.

Example 123

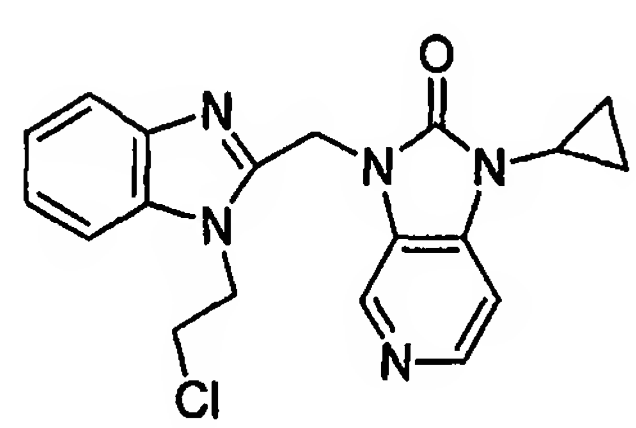


A mixture of Example **122** (38 mg, 0.10 mmol) and sodium azide (20 mg, 0.30 mmol) in DMF (2 ml) was heated to 70 °C for 2 hours. The final solution was diluted with EtOAc (10 ml) and washed with H_2O (3 x 10 ml) and brine. The combined organic extracts were dried over $MgSO_4$, concentrated, and purified by flash chromatography, (gradient, CH_2Cl_2/MeOH, 40:1 to 20:1) to yield 33 mg (85% yield) of Example **123** as a white solid.

^{1}H NMR ($CDCl_3$) δ 1.00-1.05 (m, 2 H), 1.13-1.19 (m, 2 H), 1.91-1.97 (m, 2 H), 2.90-2.94 (m, 1 H), 3.35 (t, J = 6.3 Hz, 2 H), 4.43 (t, J = 7.2 Hz, 2 H), 5.37 (s, 2 H), 7.12 (d, J = 5.2 Hz, 1 H), 7.26-7.30 (m, 2 H), 7.33-7.35 (m, 1 H), 7.77 (d, J = 7.2 Hz, 1 H), 8.32 (d, J = 5.0 Hz, 1 H), 8.72 (s, 1 H);
MS m/e 388 (MH^+);

Anal. Calcd for $C_{20}H_{20}N_8O$:	C, 61.84; H, 5.19; N, 28.84
Found:	C, 61.59; H, 5.27; N, 28.50.

Example 124

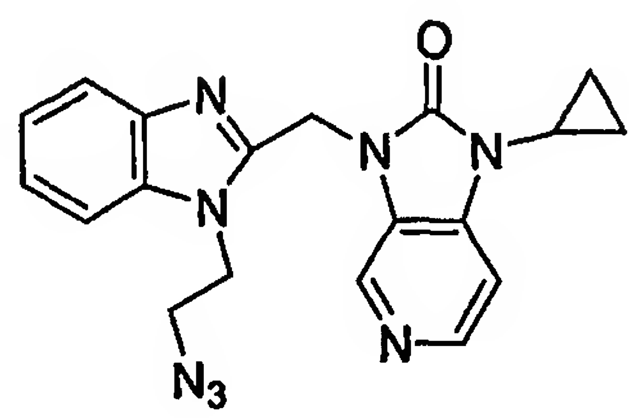


^{1}H NMR ($CDCl_3$) δ 1.02-1.05 (m, 2 H), 1.15-1.19 (m, 2 H), 2.90-2.95 (m, 1 H), 3.77 (t, J = 6.0 Hz, 2 H), 4.76 (t, J = 6.1 Hz, 2 H), 5.44 (s, 2 H), 7.14 (d, J = 5.2

Hz, 1 H), 7.28-7.32 (m, 3 H), 7.78-7.80 (m, 1 H), 8.34 (d, J = 4.8 Hz, 1 H), 8.77 (s, 1 H);

MS m/e 368 (MH^+).

Example 125



Example **125** was prepared from Example **124** according to the same procedure described for Example **123**.

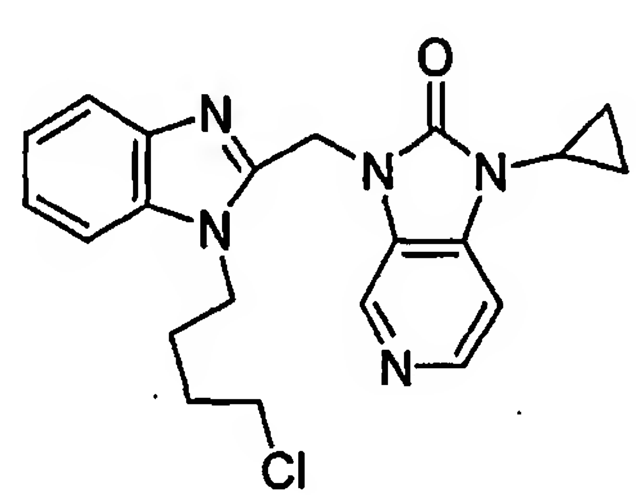
^{1}H NMR ($CDCl_3$) δ 1.01-1.06 (m, 2 H), 1.16-1.20 (m, 2 H), 2.92-2.96 (m, 1 H), 3.70 (t, J = 6.0 Hz, 2 H), 4.54 (t, J = 6.1 Hz, 2 H), 5.43 (s, 2 H), 7.15 (d, J = 5.2 Hz, 1 H), 7.29-7.32 (m, 3 H), 7.78-7.81 (m, 1 H), 8.34 (d, J = 4.8 Hz, 1 H), 8.79 (s, 1 H);

MS m/e 375 (MH^+);

Anal. Calcd for $C_{19}H_{18}N_8O$• 0.25 H_2O: C, 60.23; H, 4.92; N, 29.57

Found: C, 60.30; H, 4.85; N, 29.44.

Example 126



^{1}H NMR ($CDCl_3$) δ 1.00-1.04 (m, 2 H), 1.16-1.20 (m, 2 H), 1.79-1.81 (m, 4 H), 2.92-2.96 (m, 1 H), 3.49-3.50 (m, 2 H), 4.35 (s, 2 H), 5.37 (s, 2 H), 7.13 (d, J=5.2

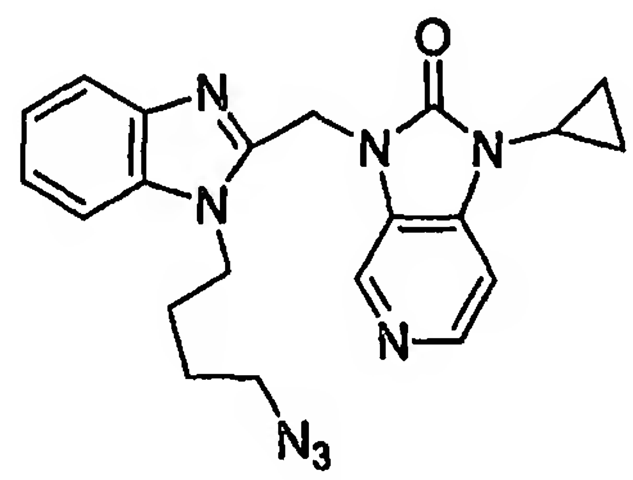
Hz, 1 H), 7.26-7.33 (m, 3 H), 7.76-7.79 (m, 1 H), 8.83 (d, J=5.2 Hz, 1 H), 8.72 (s, 1 H);

MS m/e 396 (MH^+);

Anal. Calcd for $C_{21}H_{22}ClN_5O \bullet 0.20\ H_2O$: C, 63.14; H, 5.64; N, 17.53

Found: C, 62.74; H, 5.54; N, 17.57.

Example 127

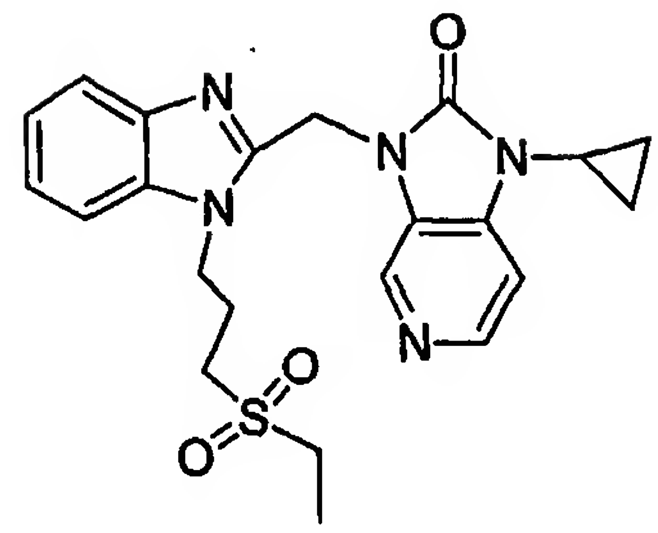


Example **127** was prepared from Example **126** according to the same procedure described for Example **123**.

^{1}H NMR ($CDCl_3$) δ 0.99-1.02 (m, 2 H), 1.15-1.19 (m, 2 H), 1.58-1.63 (m, 2 H), 1.69-1.75 (m, 2 H), 2.90-2.95 (m, 1 H), 3.27 (t, J = 6.5 Hz, 2 H), 4.32 (t, J = 7.3 Hz, 2 H), 5.35 (s, 2 H), 7.12 (d, J = 5.0 Hz, 1 H), 7.25-7.31 (m, 3 H), 7.76-7.77 (m, 1 H), 8.32 (d, J = 4.8 Hz, 1 H), 8.71 (s, 1 H);

MS m/e 403 (MH^+).

Example 128



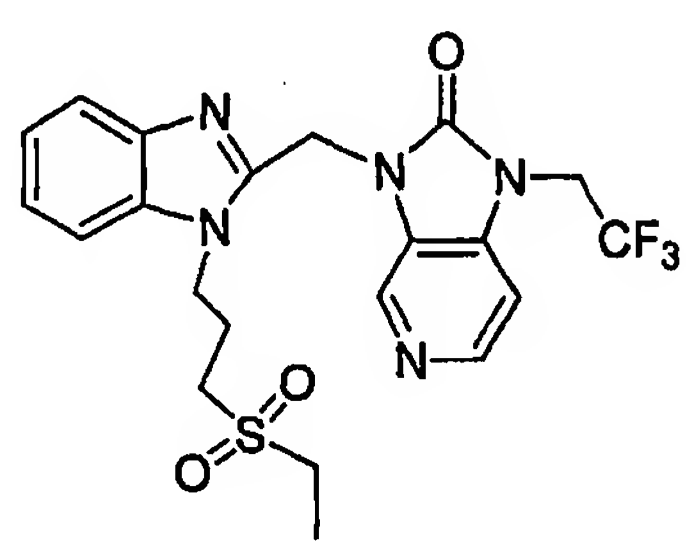
^{1}H NMR (DMSO-d_6) δ 0.91-0.94 (m, 2 H), 1.04-1.09 (m, 2 H), 1.20 (t, J = 7.5 Hz, 3 H), 2.06-2.13 (m, 2 H), 2.98-3.02 (m, 1 H), 3.11 (q, J = 7.5 Hz, 2 H), 3.16-3.21 (m, 2 H), 4.86 (t, J = 7.6 Hz, 2 H), 5.42 (s, 2 H), 7.18-7.21 (m, 1 H), 7.26-7.30 (m, 2 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 8.1 Hz, 1 H), 8.26 (d, J = 5.3 Hz, 1 H), 8.44 (s, 1 H);

IR (KBr, cm^{-1}) 3421, 1610, 1706, 1500, 1458, 1409, 1298, 1131, 751;

MS m/e 440 (MH$^+$);

Anal. Calcd for $C_{22}H_{25}N_5O_3S \bullet 2\,H_2O$:		C, 55.56; H, 6.15; N, 14.73
	Found:	C, 55.29; H, 5.89; N, 14.59.

Example 129



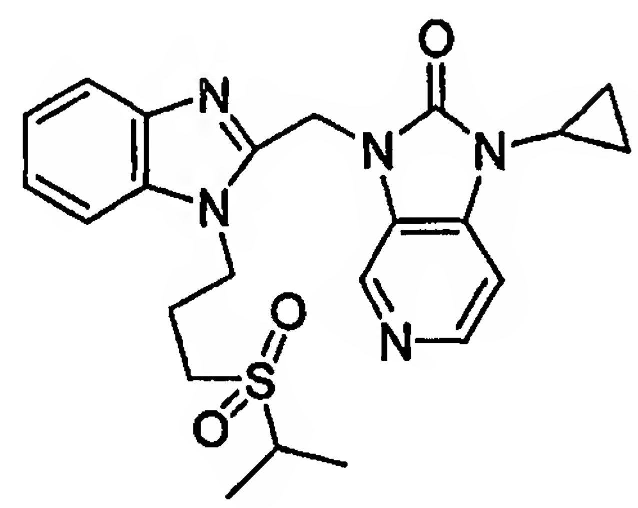
^{1}H NMR (DMSO-d_6) δ 1.21 (t, J = 7.4 Hz, 3 H), 2.14-2.16 (m, 2 H), 3.13 (q, J = 7.4 Hz, 2 H), 3.22 (t, J = 7.5 Hz, 2 H), 4.50 (t, J = 7.5 Hz, 2 H), 4.91 (q, J = 9.3 Hz, 2 H), 5.53 (s, 2 H), 7.19 (t, J = 7.7 Hz, 1 H), 7.28 (t, J = 7.7 Hz, 1 H), 7.46 (d, J = 5.3 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 8.33 (d, J = 5.0 Hz, 1 H), 8.52 (s, 1 H);

IR (KBr, cm^{-1}) 3430, 2945, 1726, 1615, 1500, 1411, 1266, 1170, 1125, 745;

MS m/e 482 (MH^+);

Anal. Calcd for $C_{21}H_{22}F_3N_5O_3S \bullet 0.25\ H_2O$:		C, 51.90; H, 4.67; N, 14.41
	Found:	C, 51.69; H, 4.74; N, 14.17.

Example 130



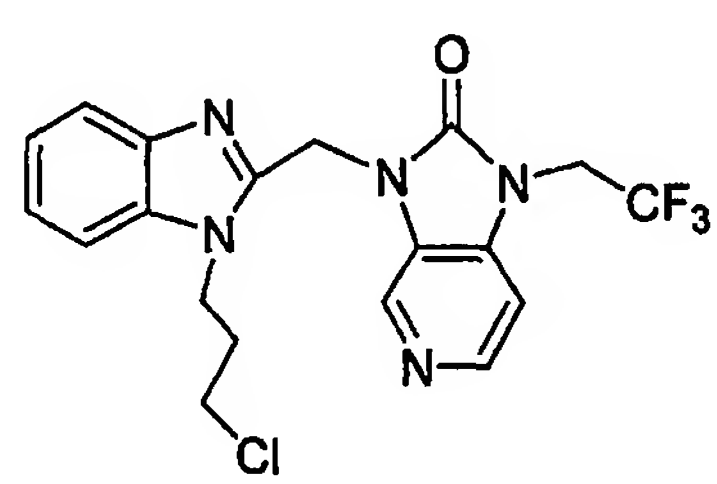
^{1}H NMR (DMSO-d_6) δ 0.92-0.93 (m, 2 H), 1.05-1.07 (m, 2 H), 1.23 (d, J=6.8 Hz, 6 H), 2.06-2.12 (m, 2 H), 2.98-3.02 (m, 1 H), 3.16-3.20 (m, 2 H), 3.28-3.30 (m, 1 H), 4.49 (t, J=7.6 Hz, 2 H), 5.42 (s, 2 H), 7.21 (t, J= 7.1 Hz, 1 H), 7.26-7.30 (m, 2 H), 7.59 (d, J=8.0 Hz, 1 H), 7.64 (d, J=8.0 Hz, 1 H), 8.25 (d, J=5.2 Hz, 1 H), 8.44 (s, 1 H);

IR (KBr, cm^{-1}) 2926, 1720, 1604, 1498, 1471, 1420, 1267, 1126, 746;

MS m/e 454 (MH^+);

Anal. Calcd for $C_{23}H_{27}N_5O_3S{\bullet}0.7\ H_2O$:		C, 59.26; H, 6.14; N, 15.02
	Found:	C, 59.58; H, 6.10; N, 14.63.

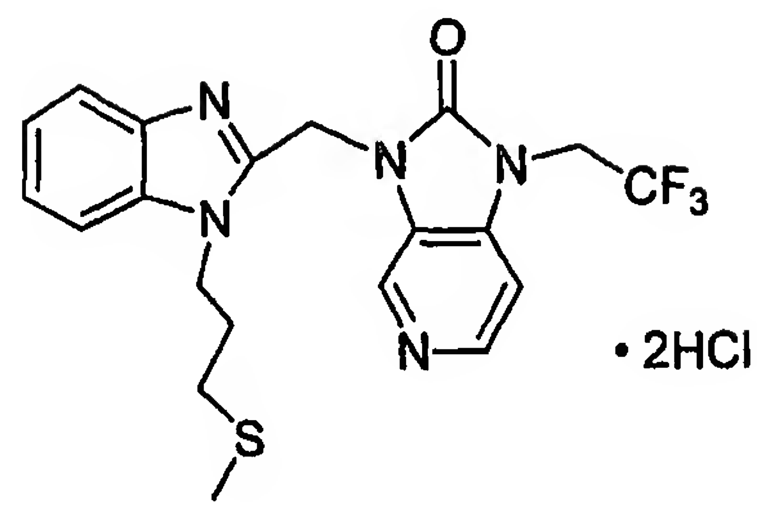
Example 131



^{1}H NMR ($CDCl_3$) δ 2.03-2.17 (m, 2 H), 3.53 (t, J = 6.2 Hz, 2 H), 4.45-4.54 (m, 4 H), 5.44 (s, 2 H), 7.01 (d, J = 5.1 Hz, 1 H), 7.24-7.32 (m, 2 H), 7.37-7.41 (m, 2 H), 7.73-7.78 (m, 1 H), 8.36 (d, J = 5.4 Hz, 1 H), 8.79 (s, 1 H);

MS m/e 424 (MH^+).

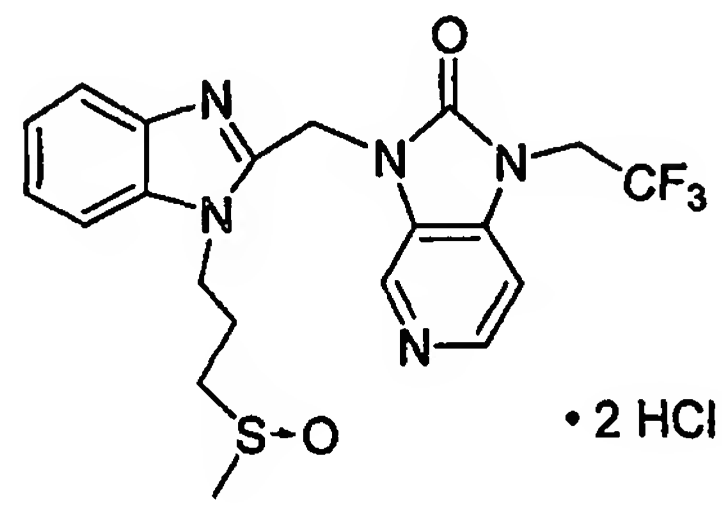
Example 132



To a volume of DMF (10 mL) saturated with excess methanethiol at –78 °C was added sodium hydride (60% suspension in mineral oil, 56 mg, 1.39 mmol). The mixture was warmed to 0 °C and stirred for 30 minutes. The mixture was then added to a solution of Example **131** (394 mg, 0.93 mmol) in DMF (2 mL) and was stirred at 0 °C for 30 minutes. The solvent was evaporated under high vacuum. The residue was neutralized with concentrated HCl and the solvent was evaporated. The residue was diluted with CH_2Cl_2 and was washed with saturated aqueous $NaHCO_3$ and H_2O, dried over $MgSO_4$, and evaporated. Purification by flash column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 10:1) gave 374 mg (93% yield) of Example **132**. Example **132** (200 mg, 0.46 mmol) was converted to the HCl salt by treating a solution of Example **132** in MeOH with excess 4N HCl in dioxane and then by evaporating the solvent to give 223 mg (96% yield).

^{1}H NMR (CD_3OD) δ 2.14 (s, 3 H), 2.30-2.39 (m, 2 H), 2.70 (t, J = 6.6 Hz, 2 H), 4.78 (t, J = 7.4 Hz, 2 H), 5.01 (q, J = 8.7 Hz, 2 H), 6.05 (s, 2 H), 7.62-7.75 (m, 2 H), 7.76 (d, J = 7.5 Hz, 1 H), 7.99-8.04 (m, 2 H), 8.71 (d, J = 6.6 Hz, 1 H), 9.09 (s, 1 H);
IR (KBr, cm^{-1}) 3412, 2762, 1760, 1655, 1624, 1519, 1264, 1169, 1119, 834, 752;
MS m/e 436 (MH^+).

Example 133

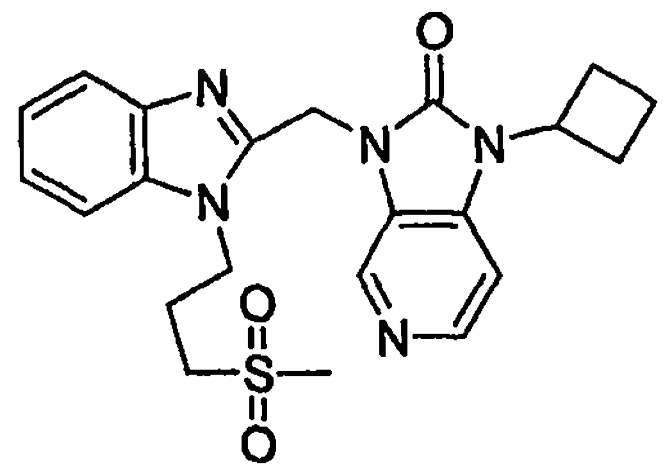


A mixture of Example **132** (174 mg, 0.40 mmol) and sodium periodate (94 mg, 0.44 mmol) in H_2O (5 mL) was stirred at 0 °C. To this mixture was added DMF (2 mL) in order to dissolve the solids and the resulting solution was stirred at room temperature for 48 hours. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$ and evaporated. Purification by flash column chromatography (gradient, straight EtOAc to EtOAc/MeOH, 5:1) gave 145 mg (81% yield) of Example **133** which was converted to the HCl salt by treating a solution of Example **133** in MeOH with 4N HCl in dioxane and then by evaporating the solvent.

^{1}H NMR (CD_3OD) δ 2.02-2.15 (m, 2 H), 2.53 (s, 3 H), 2.68 (t, J = 7.4 Hz, 2 H), 4.43-4.56 (m, 4 H), 5.43 (s, 2 H), 7.02 (d, J = 5.1 Hz, 1 H), 7.26-7.31 (m, 2 H), 7.35-7.38 (m, 1 H), 7.74-7.77 (m, 1 H), 8.35 (d, J = 5.4 Hz, 1 H), 8.79 (s, 1 H);
IR (KBr, cm^{-1}) 3412, 2854, 1760, 1656, 1624, 1519, 1264, 1169, 1120, 753;
MS m/e 452 (MH^+);

Anal. Calcd for $C_{20}H_{20}F_3N_5O_2S$•2HCl•H_20:		C, 44.29; H, 4.46; N, 12.91
	Found:	C, 44.08; H, 4.93; N, 11.54.

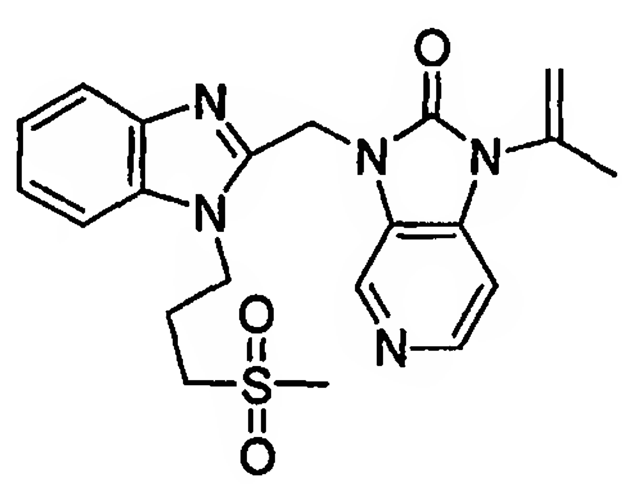
Example 135



^{1}H NMR (DMSO-d_6) δ 1.73-1.92 (m, 2 H), 2.13-2.16 (m, 2 H), 2.31-2.33 (m, 2 H), 2.79-2.83 (m, 2 H), 3.00 (s, 3 H), 3.24 (t, J = 7.7 Hz, 2 H), 4.49 (t, J = 7.4 Hz, 2 H), 4.85-4.92 (m, 1 H), 5.44 (s, 2 H), 7.19-7.20 (m,1 H), 7.26-7.27 (m, 1H), 7.49 (d, J = 5.3 Hz, 1 H), 7.57 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.05 Hz, 1 H), 8.25 (d, J = 5.3 Hz, 1 H), 8.46 (s, 1 H);
MS m/e 440 (MH^+);

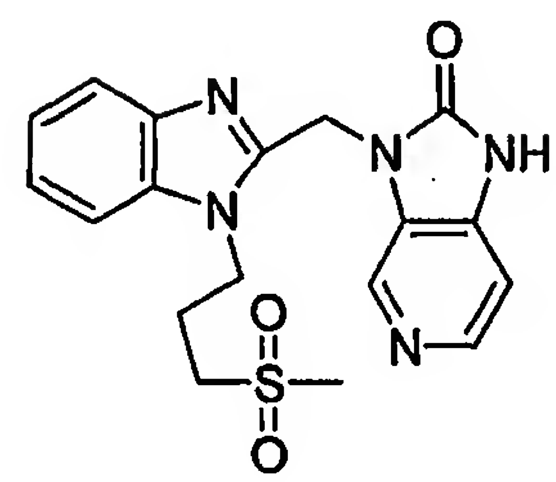
Anal. Calcd for $C_{22}H_{25}N_5O_3S$:	C, 60.11; H, 5.73; N, 15.93
Found:	C, 60.09; H, 5.76; N, 15.89.

Example 136



^{1}H NMR (DMSO-d_6) δ 2.12-2.18 (m, 5 H), 3.00 (s, 3 H), 3.24 (t, J = 7.6 Hz, 2 H), 4.51 (t, J = 7.6 Hz, 2 H), 5.45-5.48 (m, 3 H), 7.19-7.28 (m, 3 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 8.1 Hz, 1 H), 8.26 (d, J = 5.3 Hz, 1 H), 8.52 (s, 1 H);
MS m/e 426 (MH^+).

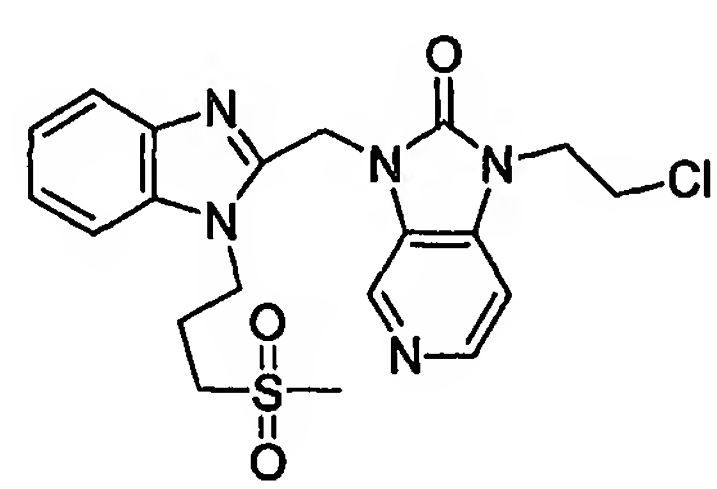
Example 137



Example **137** was prepared from Example **136** according to the same procedure described for Example **17**.

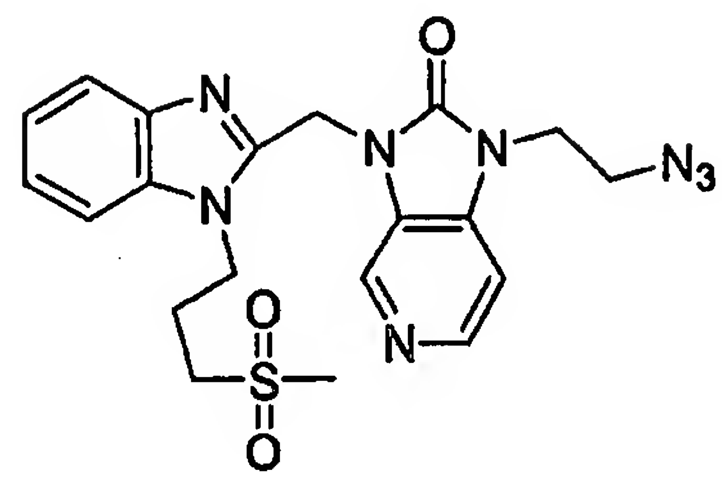
^{1}H NMR (DMSO-d_6) δ 2.12-2.16 (m, 2 H), 3.00 (s, 3 H), 3.24 (t, J = 7.6 Hz, 2 H), 4.49 (t, J = 7.6 Hz, 2 H), 5.41 (s, 2 H), 7.08 (d, J = 7.0 Hz, 1 H), 7.17-7.20 (m, 1 H), 7.25-7.29 (m, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.0 Hz, 1 H), 8.17 (d, J = 5.2 Hz, 1 H), 8.39 (s, 1 H);
MS m/e 386 (MH$^+$).

Example 138



^{1}H NMR ($CDCl_3$) δ 2.16-2.22 (m, 2 H), 2.91 (s, 3 H), 3.09 (t, J= 7.3 Hz, 2 H), 3.88 (t, J = 5.9 Hz, 2 H), 4.26 (t, J = 6.0 Hz, 2 H), 4.51 (t, J = 7.6 Hz, 2 H), 5.44 (s, 2 H), 7.20 (d, J = 5.3 Hz, 1 H), 7.28-7.34 (m, 2 H), 7.37-7.39 (m, 1 H), 7.78-7.80 (m, 1 H), 8.36 (d, J = 5 .1 Hz, 1 H), 8.78 (s, 1 H);
MS m/e 448 (MH$^+$).

Example 139



Example **139** was prepared from Example **138** according to the same procedure described for Example **123**.

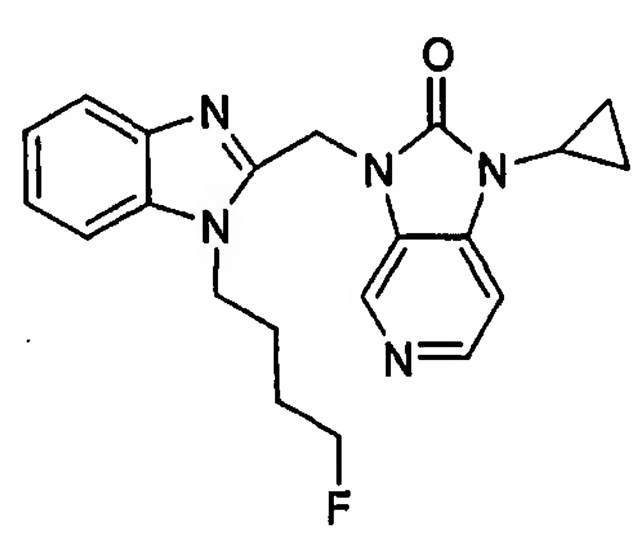
^{1}H NMR ($CDCl_3$) δ 2.18-2.24 (m, 2 H), 2.91 (s, 3 H), 3.09 (t, J = 7.3 Hz, 2 H), 3.73 (t, J = 5.9 Hz, 2 H), 4.08 (t, J = 6.0 Hz, 2 H), 4.51 (t, J = 7.6 Hz, 2 H), 5.44 (s, 2 H), 7.07 (d, J = 5.3 Hz, 1 H), 7.26-7.33 (m, 2 H), 7.33-7.38 (m, 1 H), 7.77-7.79 (m, 1 H), 8.36 (d, J = 5.1 Hz, 1 H), 8.79 (s, 1 H);

MS m/e 455 (MH^+);

Anal. Calcd for $C_{20}H_{22}N_8O_3S \bullet 0.5\ H_2O$: C, 51.83; H, 5.00; N, 24.17

Found: C, 51.85; H, 4.82; N, 23.97.

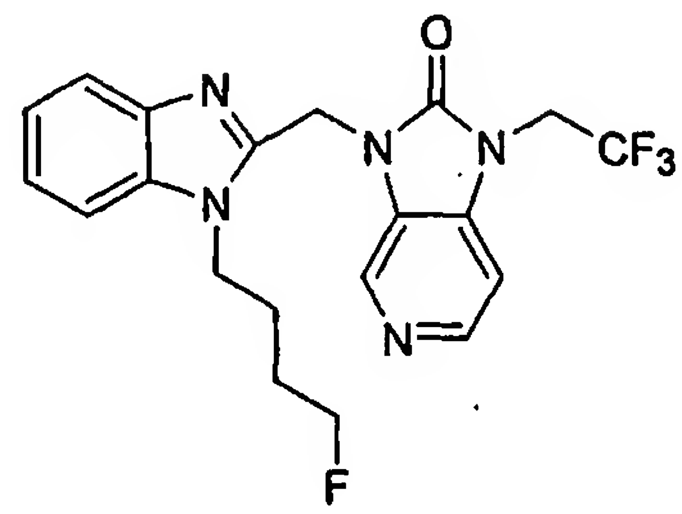
Example 140



^{1}H NMR (DMSO-d_6) δ 0.89-0.92 (m, 1 H), 1.06-1.08 (m, 1 H), 1.65-1.72 (m, 2 H), 2.96-2.99 (m, 1 H), 4.35-4.50 (m, 3 H), 5.40 (s, 2 H), 7.17-7.20 (m, 1 H), 7.24-7.29 (m, 2 H), 7.59 (d, J = 8.2 Hz, 2 H), 8.25 (d, J = 5.1 Hz, 1 H), 8.41 (s, 1 H);

MS m/e 380 (MH^+).

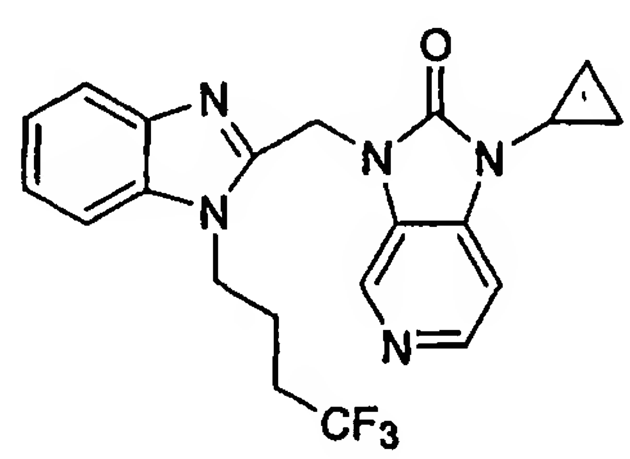
Example 141



^{1}H NMR (DMSO-d_6) δ 1.67-1.77 (m, 4 H), 4.37-4.42 (m, 3 H), 4.49-4.51 (m, 1 H), 4.92 (q, J = 9.2 Hz, 2 H), 5.50 (s, 2 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.26 (t, J = 7.7, 1 H), 7.44 (d, J = 4.3, 1 H), 7.57-7.61 (m, 2 H), 8.30-8.33 (bs, 1 H), 8.49-8.51 (bs, 1 H);

MS m/e 422 (MH^+).

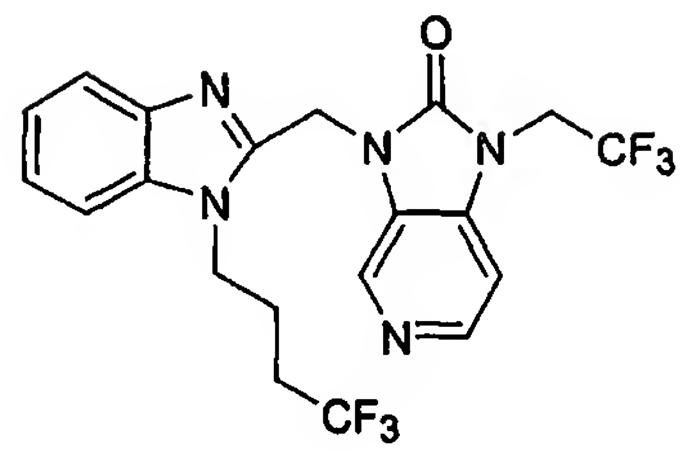
Example 142



^{1}H NMR (DMSO-d_6) δ 1.03-1.04 (m, 2 H), 1.14-1.16 (m, 2 H), 2.06-2.08 (m, 2 H), 3.11-3.18 (m, 1 H), 4.52-4.55 (m, 4 H), 5.70 (s, 2 H), 7.34-7.39 (m, 1 H), 7.43-7.47 (m, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.84 (d, J = 6.4 Hz, 2 H), 8.63 (d, J = 6.4 Hz, 1 H), 8.92 (s, 1 H);

MS m/e 416 (MH^+).

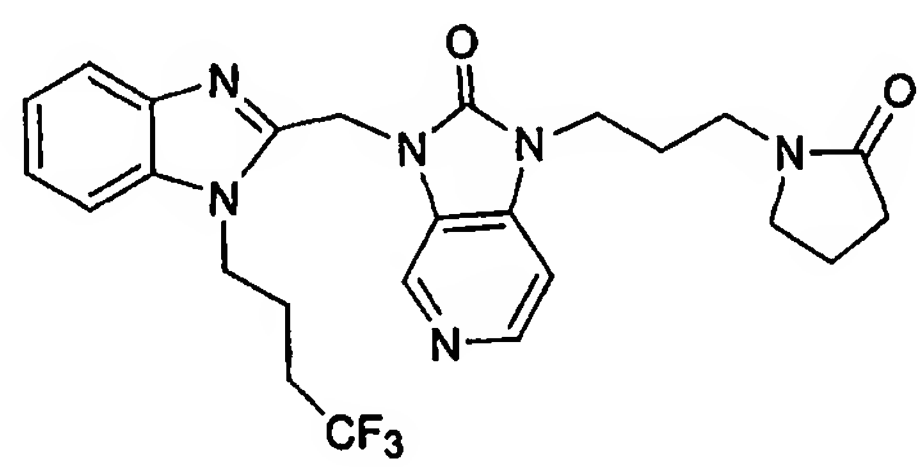
Example 143



^{1}H NMR (DMSO-d_6) δ 1.84-1.87 (m, 2 H), 4.50-4.53 (m, 4 H), 5.14 (q, J = 9.0 Hz, 2 H), 5.74 (s, 2 H), 7.30-7.32 (m, 1 H), 7.37-7.40 (m, 1 H), 7.60 (d, J = 8.2 Hz, 1 H), 7.80 (d, J = 8.0, 1 H), 8.05 (d, J = 6.2 Hz, 1 H), 8.74 (d, J = 6.3 Hz, 1 H), 9.04 (s, 1 H);

MS m/e 458 (MH^+).

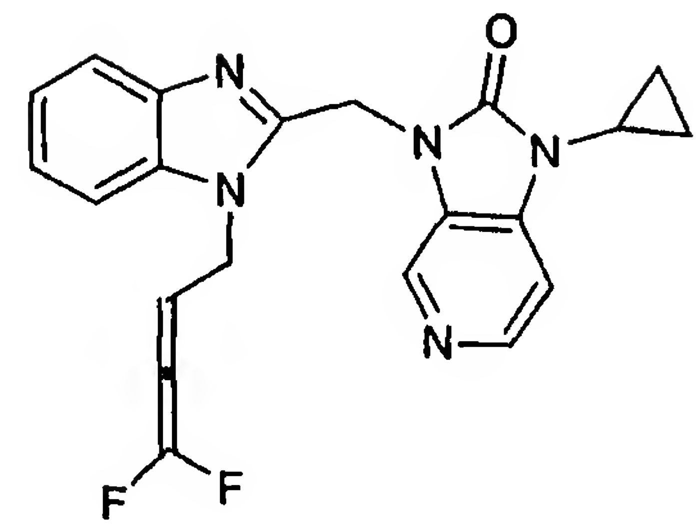
Example 144



^{1}H NMR (DMSO-d_6) δ 1.85-1.92 (m, 6 H), 2.18 (t, J = 8.1 Hz, 2 H), 2.36-2.41 (m, 2 H), 2.34 (t, J = 7.3 Hz, 2 H), 3.88 (t, J = 7.3 Hz, 2 H), 4.43 (t, J = 7.6 Hz, 2 H), 5.46 (s, 2 H), 7.19 (t, J = 7.0 Hz, 1 H), 7.27 (t, J = 7.0 Hz, 1 H), 7.38 (d, J = 5.5 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 7.9 Hz, 1 H), 8.26 (d, J = 5.2 Hz, 1 H), 8.46 (s, 1 H);

MS m/e 501 (MH^+).

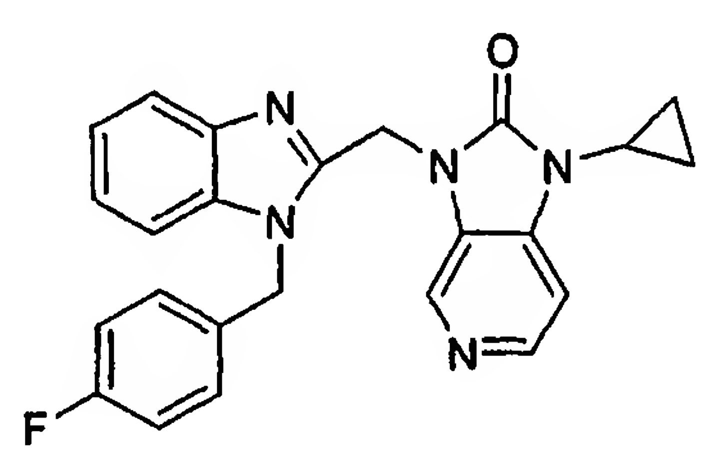
Example 145



Example **145** was prepared according to the general coupling procedure described in Scheme I-C with 4-bromo-1,1,2-trifluoro-1-butene which gave an elimination product.

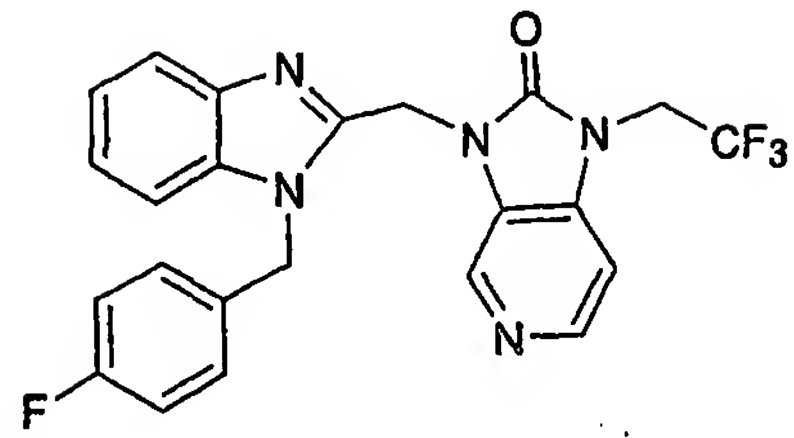
^{1}H NMR (DMSO-d_6) δ 0.96-0.99 (m, 2 H), 1.14-1.16 (m, 2 H), 3.15-3.17 (m, 1 H), 5.53 (s, 2 H), 5.72 (d, J = 11.6 Hz, 1 H), 5.81 (d, J = 17.4 Hz, 1 H), 6.77-6.86 (m, 1 H), 7.34-7.42 (m, 2 H), 7.54 (d, J = 7.9 Hz, 1 H), 7.69 (d, J = 7.9 Hz, 1 H), 7.85 (d, J = 6.4 Hz, 1 H), 8.64 (d, J = 6.1 Hz, 1 H), 8.90 (s, 1 H);
MS m/e 394 (MH^+).

Example 146



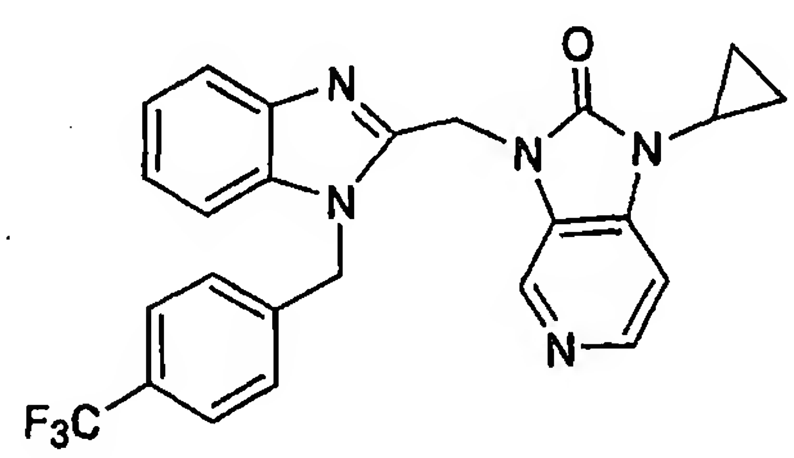
^{1}H NMR (DMSO-d_6) δ 0.64-0.66 (m, 2 H), 0.97-0.98 (m, 2 H), 2.77-2.78 (m, 1 H), 5.40 (s, 2 H), 5.59 (s, 2 H), 6.77-6.81 (m, 2 H), 6.94 (t, J = 8.9 Hz, 2 H), 7.15 (d, J = 5.2 Hz, 1 H), 7.21-7.23 (m, 2 H), 7.40-7.42 (m, 1 H), 7.68-7.70 (m, 1H), 8.20 (d, J = 5.2 Hz, 1 H), 8.31 (s, 1 H);MS m/e 413 (MH^+).

Example 147



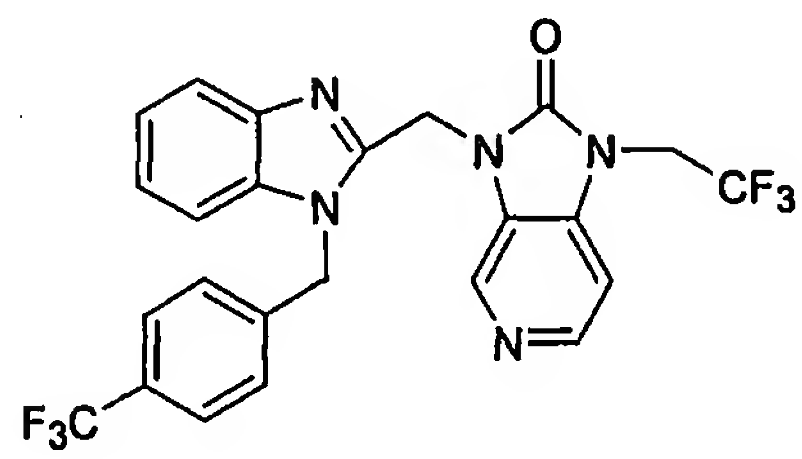
^1H NMR (DMSO-d_6) δ 4.74-4.79 (m, 2 H), 5.49 (s, 2 H), 5.60 (s, 2 H), 6.96-7.04 (m, 4 H), 7.17-7.25 (m, 2 H), 7.36 (d, J = 5.2 Hz, 1 H), 7.48 (d, J = 7.3 Hz, 1 H), 7.65 (d, J = 6.7 Hz, 1 H), 8.28 (d, J = 5.5 Hz, 1 H), 8.36 (s, 1 H);
MS m/e 456 (MH^+).

Example 148



^1H NMR (DMSO-d_6) δ 0.53-0.56 (m, 2 H), 0.92-0.96 (m, 2 H), 2.66-2.69 (m, 1 H), 5.41 (s, 2 H), 5.71 (s, 2 H), 6.83 (d, J = 8.2 Hz, 2 H), 7.06 (d, J = 5.2 Hz, 1 H), 7.23-7.25 (m, 2 H), 7.40-7.42 (m, 3 H), 7.72-7.74 (m, 1 H), 8.18 (d, J = 5.1 Hz, 1 H), 8.30 (s, 1 H);
MS m/e 464 (MH^+).

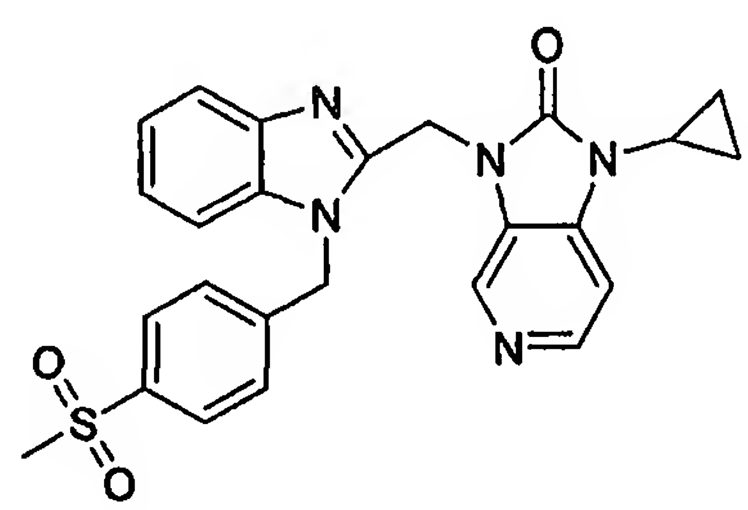
Example 149



^{1}H NMR (DMSO-d_6) δ 4.68-4.70 (m, 2 H), 5.49 (s, 2 H), 5.74 (s, 2 H), 7.04 (d, J = 8.1 Hz, 2 H), 7.22-7.23 (m, 2H), 7.31 (d, J = 5.3 Hz, 1 H), 7.40-7.50 (m, 1H), 7.51 (d, J = 8.2 Hz, 2 H), 7.64-7.70 (m, 1 H), 8.25 (d, J = 5.2 Hz, 1 H), 8.38 (s, 1 H);

MS m/e 464 (MH$^+$).

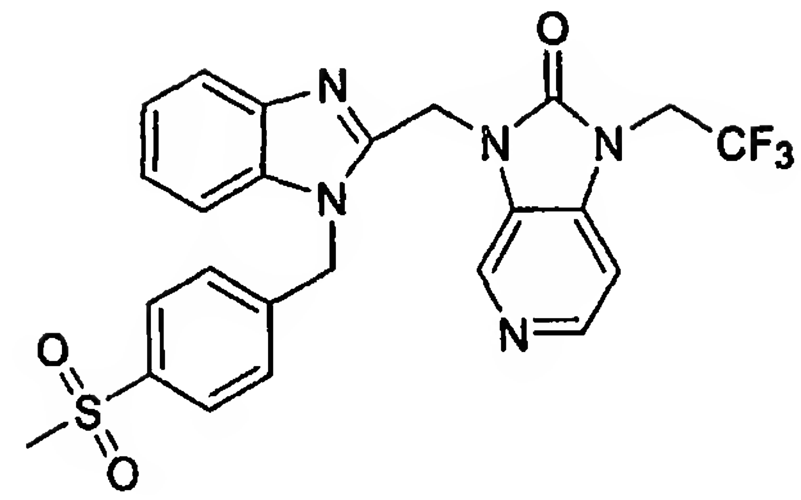
Example 150



^{1}H NMR (DMSO-d_6) δ 0.76-0.77 (m, 2 H), 1.05-1.07 (m, 2 H), 2.92-2.96 (m, 1 H), 3.56 (s, 3 H), 5.56 (s, 2 H), 5.81 (s, 2 H), 7.14 (d, J = 8.3 Hz, 2 H), 7.26-7.28 (m, 2 H), 7.47-7.49 (m, 1 H), 7.68-7.71 (m, 2 H), 7.77 (d, J = 8.4 Hz, 2 H), 8.58 (d, J = 6.4 Hz, 1 H), 8.72 (s, 1 H);

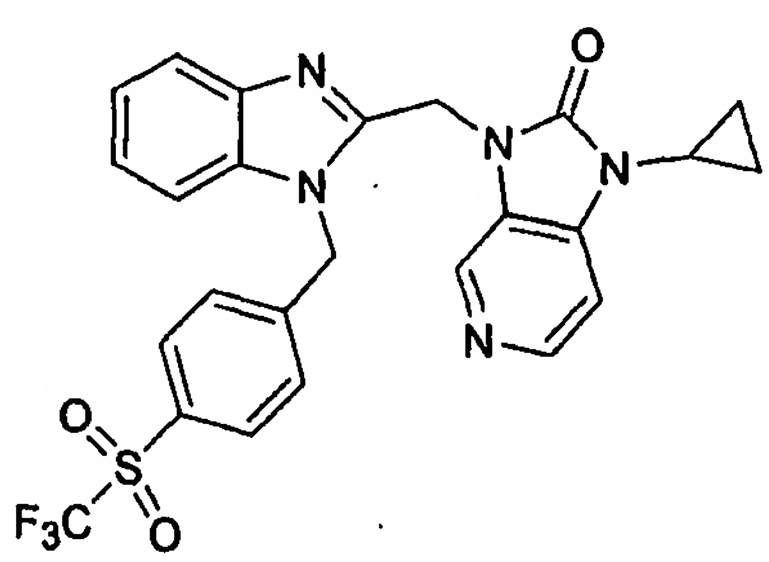
MS m/e 474 (MH$^+$).

Example 151



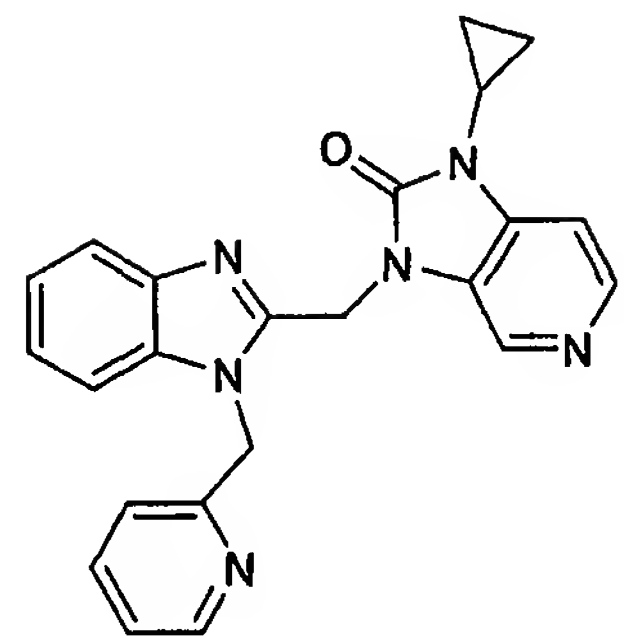
^{1}H NMR (DMSO-d_6) δ 3.20 (s, 3 H), 4.95-5.02 (m, 2 H), 5.66 (s, 2 H), 5.84 (s, 2 H), 5.56 (s, 2 H), 5.81 (s, 2 H), 7.26-7.29 (m, 2 H), 7.34 (d, J = 8.3 Hz, 2 H), 7.51-7.53 (m, 1 H), 7.64-7.66 (m, 1 H), 7.85 (d, J = 8.4 Hz, 2 H), 7.99 (d, J = 6.3 Hz, 1 H), 8.71 (d, J = 6.4 Hz, 1 H), 8.93 (s, 1 H);
MS m/e 516 (MH^+).

Example 152



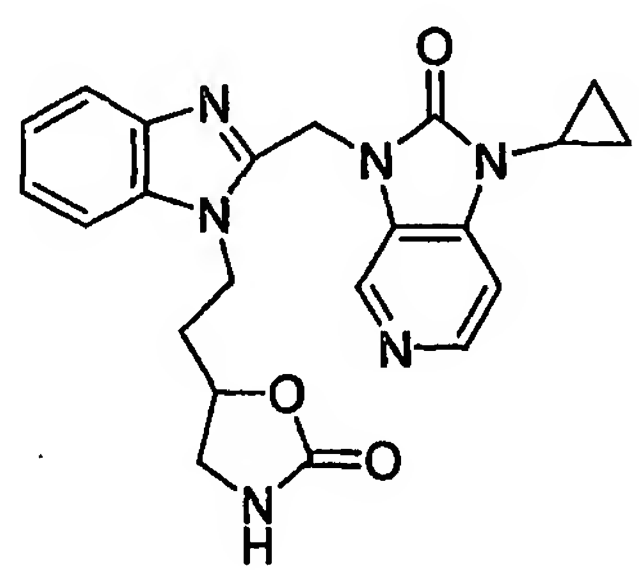
^{1}H NMR (DMSO-d_6) δ 0.78-0.81 (m, 2 H), 1.05-1.09 (m, 2 H), 2.95-2.98 (m, 1 H), 5.60 (s, 2 H), 5.95 (s, 2 H), 7.30 (dd, J = 3.0, 6.1 Hz, 2 H), 7.39 (d, J = 8.6 Hz, 2 H), 7.48-7.51 (m, 2 H), 7.71 (dd, J = 3.0, 6.1 Hz, 2 H), 7.73 (d, J = 6.4 Hz, 1 H), 8.04 (d, J = 8.6 Hz, 1 H), 8.60 (d, J = 6.4 Hz, 1 H), 8.82 (s, 1 H);
MS m/e 528 (MH^+).

Example 153



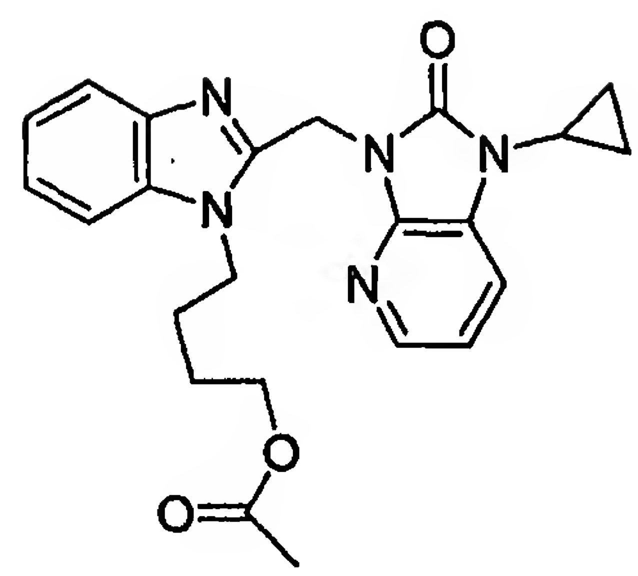
^{1}H NMR (DMSO-d_6) δ 0.68-0.71 (m, 2 H), 0.96-1.00 (m, 2 H), 2.79-2.82 (m, 1 H), 5.49 (s, 2 H), 5.69 (s, 2 H), 7.02 (d, J = 7.9 Hz, 1 H), 7.16-7.21 (m, 4 H), 7.43-7.45 (m, 1 H), 7.59-7.65 (m, 2 H), 8.21 (d, J = 5.0 Hz, 1 H), 8.24 (d, J = 3.9 Hz, 1 H), 8.35 (s, 1 H);

Example 154



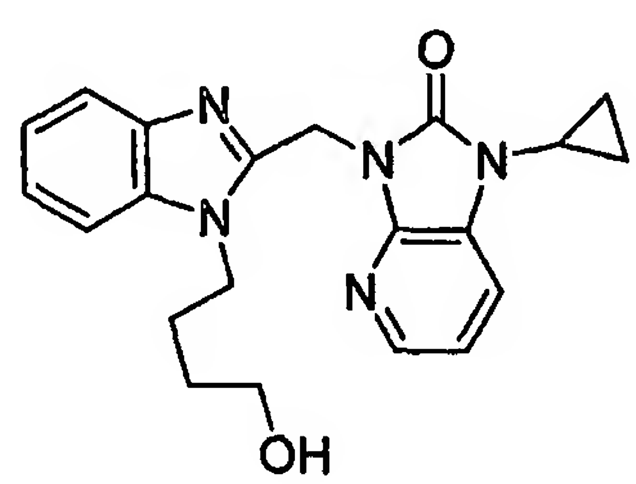
^{1}H NMR (CD_3OD) δ 1.16-1.20 (m, 2 H), 1.21-1.27 (m, 2 H), 2.44-2.48 (m, 1 H), 2.51-2.56 (m, 1 H), 3.18-3.22 (m, 1 H), 3.32-3.34 (m, 1 H), 3.74-3.78 (m, 1 H), 4.73-4.78 (m, 1 H), 4.81-4.89 (m, 2 H), 6.01 (d, 2 H), 7.63-7.67 (m, 1 H), 7.68-7.72 (m, 1 H), 7.79 (d, J=8.2 Hz, 1 H), 7.94 (d, J=6.4 Hz, 1 H), 8.02 (d, J=8.3 Hz, 1 H), 8.61 (d, J=6.4 Hz, 1 H), 8.96 (s, 1 H);
MS m/e 419 (MH^+).

Example 155



^{1}H NMR ($CDCl_3$) δ 1.00-1.03 (m, 2 H), 1.08-1.12 (m, 2 H), 1.68-1.74 (m, 2 H), 1.84-1.90 (m, 2 H), 2.06 (s, 3 H), 3.47-3.51 (m, 2 H), 4.09 (t, J=6.3 Hz, 2 H), 4.46 (t, J=7.5 Hz, 2 H), 5.42 (s, 2 H), 6.99-7.01 (m, 1 H), 7.20-7.27 (m, 2 H), 7.33-7.37 (m, 2 H), 7.76 (d, J=7.6 Hz, 1 H), 8.06-8.07 (m, 1 H);
MS m/e 420 (MH^+).

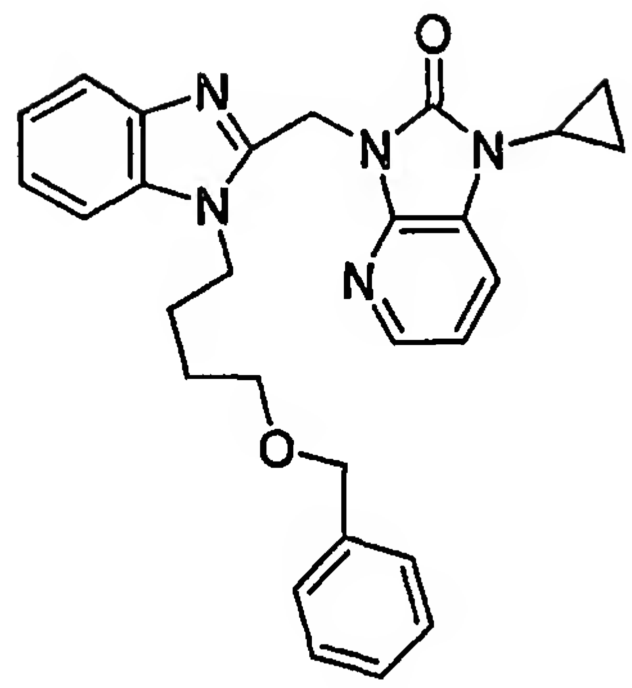
Example 156



Example **156** was prepared from Example **155** according to the same procedure described for Example **73**.

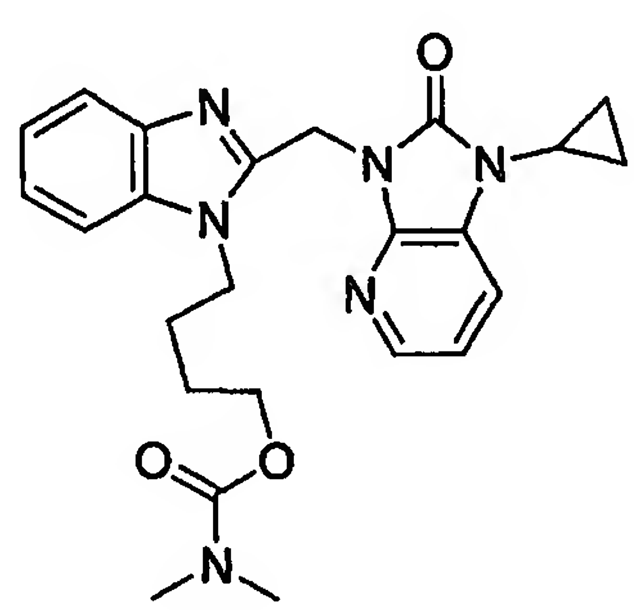
^{1}H NMR (CD_3OD) δ 1.01-1.04 (m, 2 H), 1.13-1.68 (m, 2 H), 1.63-1.68 (m, 2 H), 1.94-2.01 (m, 2 H), 2.68 (s, 3 H), 3.01-3.04 (m, 1 H), 3.60 (t, J=6.2 Hz, 2 H), 4.69 (t, J=7.9 Hz, 2 H), 5.73 (s, 2 H), 7.19-7.22 (m, 1 H), 7.63-7.69 (m, 3 H), 7.74-7.76 (m, 1 H), 7.98 (d, J=7.6 Hz, 1 H), 8.03-8.04 (m, 1 H);
MS m/e 478 (MH^+);
Anal. Calcd for $C_{21}H_{23}N_5O_2$•CH_4O_3S•0.75 H_2O: C, 54.21; H, 5.85; N, 14.22
Found: C, 54.25; H, 5.90; N, 14.38.

Example 157



^1H NMR ($CDCl_3$) δ 0.98-1.01 (m, 2 H), 1.07-1.10 (m, 2 H), 1.65-1.71 (m, 2 H), 1.84-1.90 (m, 2 H), 2.86-2.90 (m, 1 H), 3.47-3.51 (m, 2 H), 4.43 (t, J=7.6 Hz, 2 H), 4.47 (s, 2 H), 5.37 (s, 2 H), 6.97-6.99 (m, 1 H), 7.18-7.33 (m, 9 H), 7.72-7.74 (m, 1 H), 8.03-8.06 (m, 1 H);
MS m/e 468 (MH^+).

Example 158

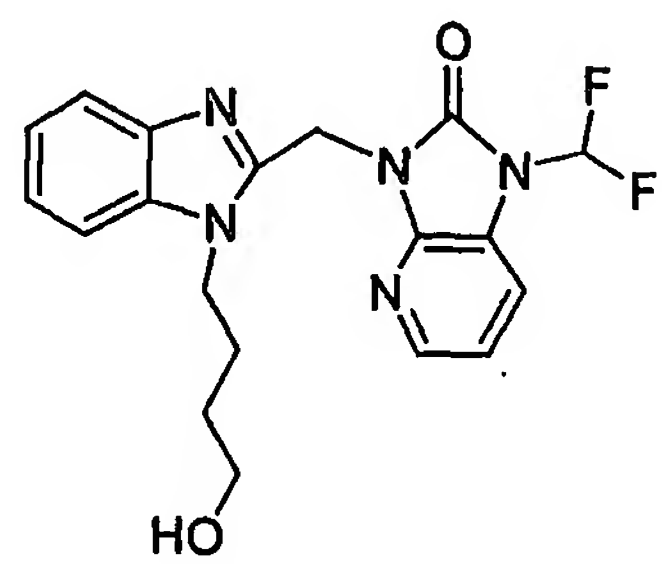


To a suspension of Example **156** (52 mg, 0.14 mmol) and sodium hydride (6.6 mg, 0.16 mmol) in DMF (2 mL) was added N,N-dimethylcarbamoyl chloride (16.2 mg, 0.15 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 12 hours. The mixture was diluted with EtOAc and washed with water. The organic extracts were dried with $MgSO_4$ and evaporated. The residue was purified by flash chromatography (gradient, CH_2Cl_2/MeOH, 40:1 to 20:1) to give 35 mg (56% yield) of Example **158** as a off-white solid.

^{1}H NMR ($CDCl_3$) δ 1.00-1.03 (m, 2 H), 1.08-1.12 (m, 2 H), 1.68-1.74 (m, 2 H), 1.84-1.90 (m, 2 H), 2.84 (s, 3 H), 2.90-2.93 (m, 4 H), 4.09 (t, J=6.3 Hz, 2 H), 4.46 (t, J=7.5 Hz, 2 H), 5.42 (s, 2 H), 6.99-7.01 (m, 1 H), 7.20-7.27 (m, 2 H), 7.33-7.37 (m, 2 H), 7.76 (d, J=7.6 Hz, 1 H), 8.06-8.07 (m, 1 H);

MS m/e 449 (MH^+).

Example 159



Example **159** was prepared via synthesis of the acetate intermediate according to the same procedure described for Example **72** followed immediately by deprotection of the alcohol according to the same procedure described for Example **73**.

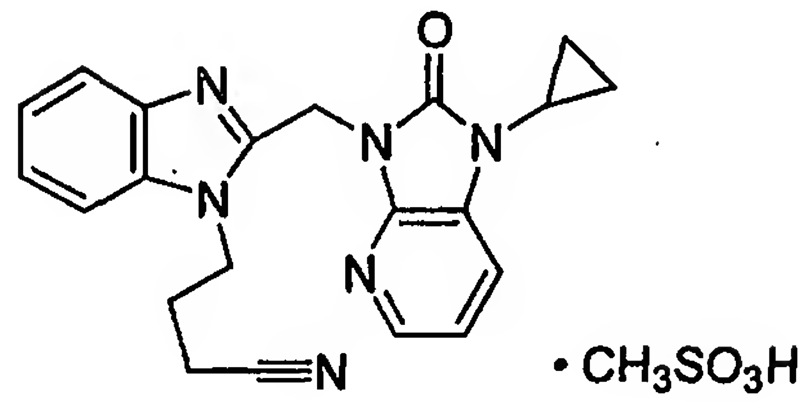
^{1}H NMR (d_6-DMSO) δ 1.44-1.54 (m, 2 H), 1.77-1.86 (m, 2 H), 3.41 (t, J = 6.3 Hz, 2 H), 4.46 (t, J = 7.2 Hz, 2 H), 5.53 (s, 2 H), 7.21 (dd, J = 5.3, 8.0 Hz, 1 H), 7.28-7.40 (m, 2 H), 7.59 (d, J = 7.8 Hz, 1 H), 7.76 (d, J = 7.8 Hz, 2 H), 7.84 (t, J = 57.6 Hz, 1 H), 8.10 (d, J = 4.8 Hz, 1 H);

IR (KBr, cm^{-1}) 3275, 2941, 1751, 1623, 1606, 1466, 2503, 1031, 772, 746;

MS m/e 388 (MH^+);

Anal. Calcd for $C_{19}H_{19}F_2N_5O_2 \bullet 0.25\ H_2O$:	C, 58.23; H, 5.02; N, 17.87
Found:	C, 58.42; H, 4.79; N, 17.64.

Example 160



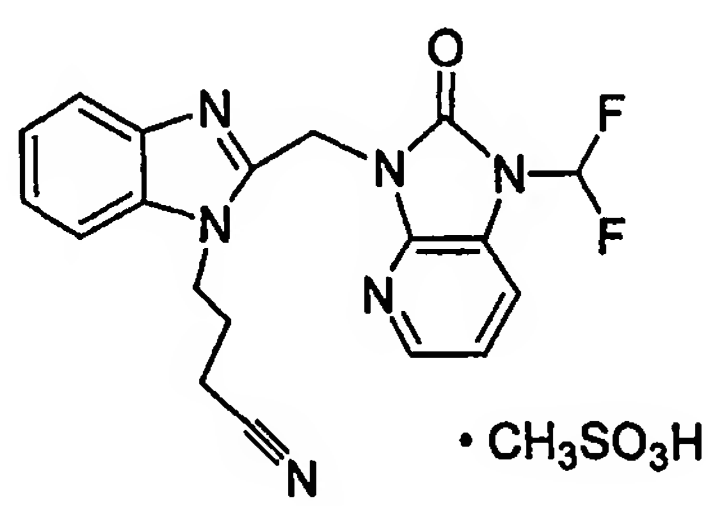
^1H NMR (CD_3OD) δ 1.02-1.05 (m, 2 H), 1.11-1.17 (m, 2 H), 2.32-2.38 (m, 2 H), 2.68 (s, 3 H), 2.71 (t, J = 7.2 Hz, 2 H), 3.01-3.05 (m, 1 H), 5.79 (s, 2 H), 7.20-7.22 (m, 1 H), 7.64-7.76 (m, 4 H), 7.99-8.05 (m, 2 H);

MS m/e 373 (MH^+);

Anal. Calcd for $C_{19}H_{18}N_8O$•1.0 H_2O•1.0 CH_4SO_3: C, 54.31; H, 5.39; N, 17.27

Found: C, 54.58; H, 5.37; N, 17.37.

Example 161



^1H NMR (CD_3OD) δ 2.37-2.40 (m, 2 H), 2.68 (s, 3 H), 2.73 (t, J = 7.3 Hz, 2 H), 4.82 (t, J = 7.6 Hz, 2 H), 5.80 (s, 2 H), 7.26-7.28 (m, 1 H), 7.62 (t, J = 58.0 Hz, 1 H), 7.65-7.79 (m, 4 H), 8.00 (d, J = 8.3 Hz, 1 H), 8.17 (dd, J = 1.3, 5.3 Hz, 1 H);

IR (KBr, cm^{-1}) 3449, 3064, 2953, 1758, 1466, 1410, 1230, 1156, 1048, 771, 551;

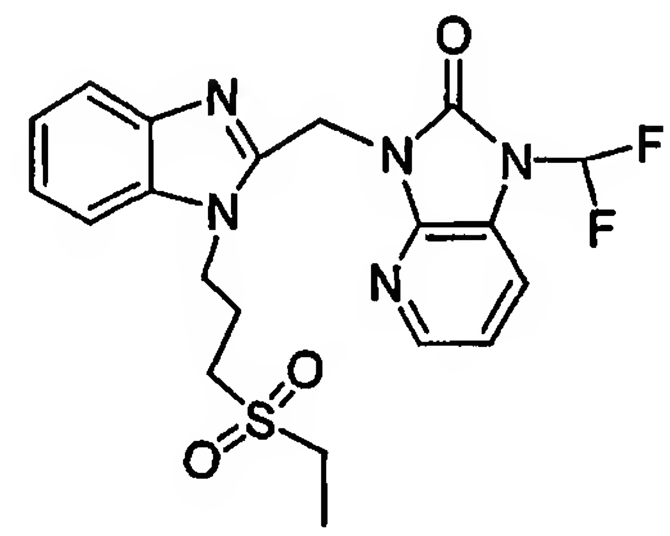
MS m/e 383 (MH^+);

Anal. Calcd for $C_{19}H_{16}F_2N_6O$•0.5 H_2O•1.0 CH_3SO_3H:

C, 49.28; H, 4.34; N, 17.24

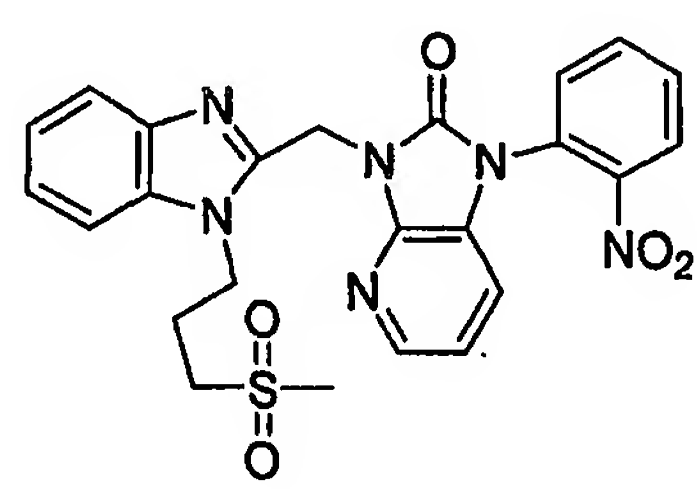
Found: C, 49.36; H, 4.42; N, 16.95.

Example 162



^1H NMR (CD_3OD) δ 1.35 (t, J = 7.5 Hz, 3 H), 2.50-2.57 (m, 2 H), 3.15 (q, J = 7.5 Hz, 2 H), 3.35 (t, J = 7.2 Hz, 2 H), 4.86 (t, J = 7.2 Hz, 2 H), 5.77 (s, 2 H), 7.24-7.27 (m, 1 H), 7.59-7.68 (m, 3 H), 7.62 (t, J = 58.0 Hz, 1 H), 7.71 (d, J = 8.3 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 1 H), 7.98 (d, J = 8.1 Hz, 1 H), 8.16 (d, J = 5.2 Hz, 1 H); MS m/e 450 (MH^+).

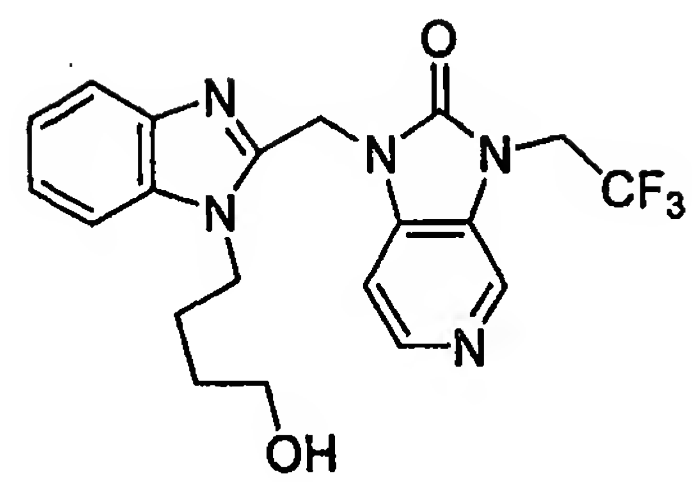
Example 163



^1H NMR (DMSO-d_6, 65 ^0C) δ 2.81-2.34 (m, 2 H), 2.99 (s, 3 H), 3.28 (t, J = 7.7 Hz, 2 H), 4.57 (t, J = 7.4 Hz, 2 H), 5.50 (s, 2 H), 7.14-7.19 (m, 2 H), 7.25-7.27 (m, 1 H), 7.41 (d, J = 8.0 Hz, 1 H), 7.53 (d, J = 7.9 Hz, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.80-7.84 (m, 1 H), 7.91 (d, J=7.6 Hz, 1 H), 7.98-8.02 (m, 1 H), 8.09 (d, J=5.0 Hz, 1 H), 8.25-8.27 (m, 1 H);

MS m/e 507 (MH^+).

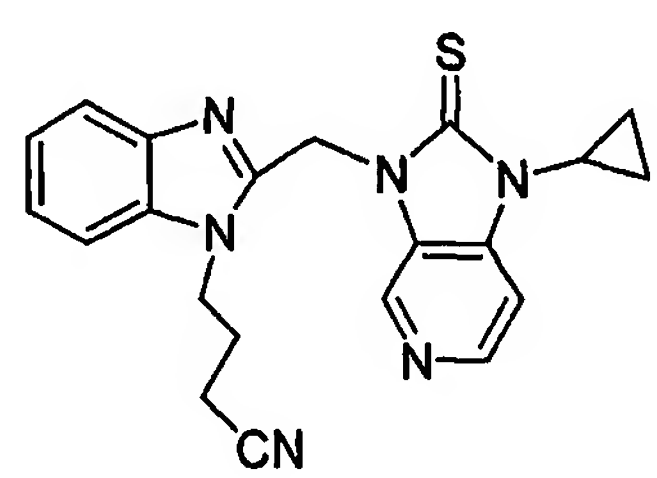
Example 164



Example **164** was prepared via synthesis of the acetate intermediate according to the same procedure described for Example **72** followed immediately by deprotection of the alcohol according to the same procedure described for Example **73**.

^{1}H NMR ($CDCl_3$) δ 1.60-1.65 (m, 2 H), 1.73-1.80 (m, 2 H), 3.64-3.70 (m, 2 H), 4.33 (t, J=8.0 Hz, 2 H), 4.53-4.60 (m, 2 H), 5.44 (s, 2 H), 7.24-7.37 (m, 3 H), 7.60 (d, J=5.3 Hz, 1 H), 7.77-7.81 (m, 1 H), 8.35-8.38 (m, 2 H);
MS m/e 420 (MH^+).

Example 165

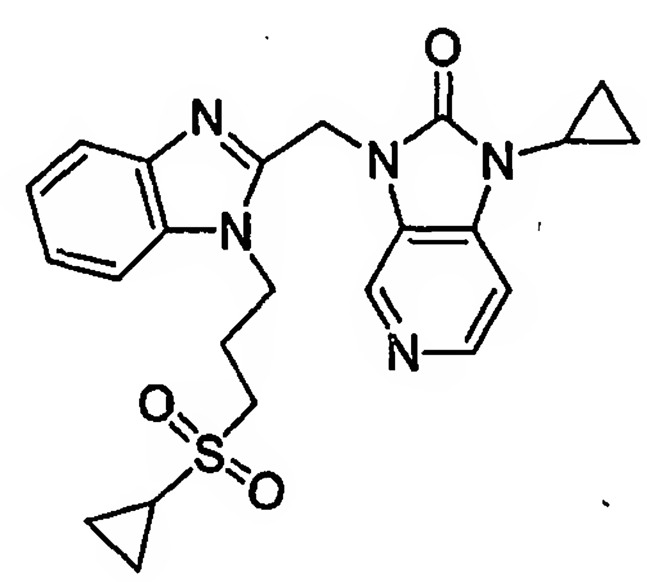


A mixture of Example **26** (100 mg, 0.27 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent, 130 mg, 0.32 mmol) in a mixture of toluene and dioxane (9:1 ratio, 10 mL) was heated in a sealed tube at 130 ^{0}C for 15 hours. The solvents were removed *in vacuo* and the residue was suspended in H_2O and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by preparative TLC (5% MeOH in CH_2Cl_2), followed by

trituration from Et_2O to give 5 mg (5 % yield) of Example **165** as an off white solid.

^{1}H NMR (DMSO-d_6) δ 1.05-1.10 (m, 2 H), 1.21-1.25 (m, 2 H), 2.07-2.15 (m, 2 H), 2.67 (t, J = 7.4 Hz, 2 H), 3.23-3.26 (m, 1 H), 4.49 (t, J = 7.5 Hz, 2 H), 5.90 (s, 2 H), 7.18 (t, J = 7.5 Hz, 1 H), 7.27 (t, J = 7.5 Hz, 1 H), 7.53 (d, J = 7.9 Hz, 1 H), 7.59 (d, J = 5.5 Hz, 1 H), 7.63 (d, J = 7.9 Hz, 1 H), 8.42 (d, J = 5.5 Hz, 1 H), 8.76 (s, 1 H);
MS m/e 389 (MH^+).

Example 166



^{1}H NMR ($CDCl_3$) δ 1.00-1.07 (m, 4 H), 1.15-1.18 (m, 2 H), 1.16-1.23 (m, 2 H), 2.20-2.26 (m, 2 H), 2.32-2.38 (m, 1 H), 2.96-2.30 (m, 1 H), 3.09 (t, J = 7.2 Hz, 2 H), 4.53 (t, J = 7.5 Hz, 2 H), 5.38 (s, 2 H), 7.18 (d, J = 5.3 Hz, 1 H), 7.27-7.33 (m, 2 H), 7.38-7.39 (m, 1 H), 7.77-7.79 (m, 1 H), 8.34 (d, J = 5.3 Hz, 1 H), 8.74 (s, 1 H);
MS m/e 452 (MH^+).

The compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), intranasally, by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating viral infections such as RSV infection. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-effective amount of a compound of the present invention.

The pharmaceutical composition may be in the form of orally-administrable suspensions or tablets; nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweetners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The compounds of this invention can be administered orally to humans in a dosage range of 0.1 to 100 mg/kg body weight in divided doses. One preferred dosage range is 0.1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 0.1 to 20 mg/kg body weight orally in divided doses. It will be understood, however, that the specific dose level and frequency of dosage

for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

BIOLOGICAL ACTIVITY

The antiviral activity of these compounds against respiratory syncytial virus was determined in HEp-2 (ATCC CCL 23) cells that were seeded in 96 well microtiter plates at 1.5×10^4 cells/100 μL/well in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with penicillin, streptomycin, glutamine, and 10% fetal bovine serum. The cells were incubated overnight at 37 °C, the culture medium was removed, and cells were infected (100 μL volume in medium containing 2% fetal bovine serum) with respiratory syncytial virus Long strain at 5000 plaque forming units/mL. The compounds, 100 μL at appropriate dilution, were added to the cells 1 hour post infection. After incubation for 4 days at 37 °C, the plates were stained with MTT solution (3-[4,5-dimethlythiazol-2-yl]-2,5-diphenyltetrazolium bromide) and incubated for 4 hours at 37 °C. The media was aspirated from the cells and 100 μL/well of acidified isopropanol (per liter: 900 mL isopropanol, 100 mL Triton X100, and 4 mL conc. HCl) was added. Plates were incubated for 15 minutes at room temperature with shaking, and an optical density (OD 540) reading at 540 nanometer (nm) was obtained. The optical density reading is proportional to the number of viable cells. The increase in the number of viable cells reflects the protective, antiviral activity of the compound. Assays comparing MTT staining in uninfected cells containing compound with uninfected cells in the absence of compound provide a measure of cellular toxicity. The control compound in this assay is Ribavirin which exhibits 100% cell protection at 2.5 μg/mL (corresponding to 10.2 μM).

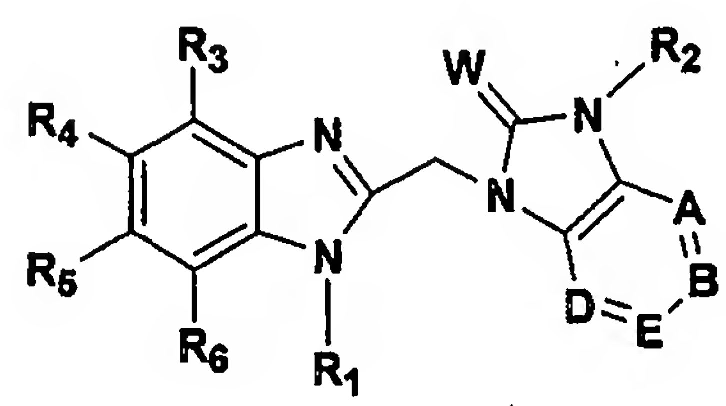
The antiviral activity of compounds, designated as EC_{50}, is presented as a concentration that produces 50% cell protection in the assay. The compounds

disclosed in this application show antiviral activity with EC_{50}'s between 50 μM and 0.001 μM. Ribavirin has an EC_{50} of 3 μM.

CLAIMS

What is claimed is:

1. A compound having the Formula I, and pharmaceutically acceptable salts thereof,



Formula I

wherein:

W is O or S;

R_1 is $-(CR'R'')_n-X$;

X is H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR'''', NR'R'', NR'COR'', NR'CONR''R''', NR'SO_2R'', NR'COOR'', COR', CR'''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', PO(OR')$_2$, aryl, heteroaryl or non-aromatic heterocycle;

m is 0-2; n is 2-6;

R_2 is

(i) H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl,

$-(CH_2)_t$ C_{3-7} cycloalkyl, $-(CH_2)_t$ C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; SO_2R'', $SO_2NR'R''$ or CN; wherein t is 1-6;

(ii) $-(CR'R'')_{n'}-Y$, wherein Y is CN, OR', OCONR'R'', NR'R'', NCOR', $NR'SO_2R''$, NR'COOR'', NR'CONR''R''', COR', CR'''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', $SO_2NR'R''$ or $PO(OR')_2$; wherein

m is 0-2 and n' is 1-6;

(iii) $-(CR'R'')_{n''}-C_6H_4-Z$, wherein the Z group may be in the ortho, meta or para position relative to the $-(CH_2)_{n''}$ group; Z is CN, OR', OCONR'R'', NO_2, NR'R'', NCOR', $NR'SO_2R''$, NR'COOR'', NR'CONR''R''', COR', CR'''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', $SO_2NR'R''$ or $PO(OR')_2$;

m is 0-2; n'' is 0-6; or

(iv) -(CR'R'')n'''-heteroaryl, wherein n''' is 0-6;

(v) -(CR'R'')n'''-non-aromatic heterocycle, wherein n''' is 0-6;

R_3, R_4, R_5 and R_6 are each independently hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkyl substituted with one to six of the same or different halogen atoms, OR', CN, COR', COOR', CONR'R'', or NO_2;

A, B, E, D are each independently C-H, C-Q-, N, or N-O; provided at least one of A, B, E or D is not C-H or C-Q; wherein Q is halogen, C_{1-3} alkyl or C_{1-3} alkyl substituted with one to three of the same or different halogen atoms; and

R', R'', R''' are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or

different halogen atoms;or R' and R" taken together form a cyclic alkyl group having 3 to 7 carbon atoms; benzyl, or aryl;

R"" is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, NR'R", CR'NR"R"', aryl, heteroaryl, non-aromatic heterocycle; and

Non-aromatic heterocycle is a 3-7 membered non-aromatic ring containing at least one and up to 4 non-carbon atoms selected from the group consisting of O, S, N, and NR';

Aryl is phenyl, naphthyl, indenyl, azulenyl, fluorenyl and anthracenyl;

Heteroaryl is a 4-7 membered aromatic ring which contains one to five heteroatoms independently selected from the group consisting of O, S, N or NR', wherein said aromatic ring is optionally fused to group B';

B' is an aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl;

Aryl, B', said 4-7 membered aromatic ring, and said 3-7 membered non-aromatic ring may each independently contain one to five substituents which are each independently selected from R_7, R_8, R_9, R_{10} or R_{11}; and

R_7, R_8, R_9, R_{10} and R_{11} are each independently

(i) H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; and

(ii) halogen, CN, NO_2, OR', NR'R'', COR', COOR', CONR'R'', OCOR', NR'COR'', SO_mR', $SO_2NR'R''$, $PO(OR')_2$.

2. The compound of claim 1 wherein heteroaryl is selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-oxadiazol-5-one, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, tetrazole and phenoxazinyl.

3. A compound of claim 2 wherein:

R_1 is $-(CH_2)_n$-X;

X is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; halogen, CN, OR', OCOR'''', NR'R'', NR'COR'', NR'COOR'', COR', CR'''NNR'R'', CR'NOR'', COOR', CONR'R'', SO_mR', aryl or heteroaryl;

m is 0-2; n is 2-4;

R_2 is

(i) H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, $-(CH_2)_t$ C_{3-7} cycloalkyl, $-(CH_2)_t$ C_{4-7} cycloalkenyl, each of said alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl being optionally substituted with one to six of the same or different halogen atoms; SO_2R'', $SO_2NR'R''$ or CN; wherein t is 1-6;

(ii) $-(CH_2)_{n'}$-Y, wherein Y is CN, OR', COR', COOR', CONR'R'', SO_mR', $SO_2NR'R''$, $PO(OR')_2$ wherein m is 0-2 and n' is 1-6; or

(iii) $-(CH_2)n''-C_6H_4$-Z, wherein the Z group may be in the ortho, meta or para position relative to the $-(CH_2)n''$ group; Z is CN, OR', COR' or SO_mR'; m is 0-2; n'' is 0-3;

R_3, R_4, R_5, and R_6 are each independently hydrogen, halogen, C_{1-6} alkyl, optionally substituted with one to six of the same or different halogen atoms; and

A, B, E, D are each independently C-H or N; provided at least one of A, B, E or D is not C-H.

4. A compound of claim 2 wherein:

R_3, R_4, R_5 and R_6 are each H;

A, B and D are each C-H; and

E is N.

5. A compound of claim 2 wherein:

R_3, R_4, R_5 and R_6 are each H;

A, B and E are each C-H; and

D is N.

6. A method for treating mammals infected with RSV, and in need thereof, which comprises administering to said mammal a therapeutically effective amount of a compound having the Formula I, and pharmaceutically acceptable salts thereof, as claimed in any one of claims 1-5.

7. A pharmaceutical composition which comprises a therapeutically effective amount of an anti-RSV compound having Formula I, and pharmaceutically acceptable salts thereof, as claimed in any one of claims 1-5, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/14775

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/495, 31/50, 31/52, 31/44; A61P 31/12; C07D 471/02, 473/30, 487/02
US CL : 514/248, 249, 262, 303; 544/236, 265, 276, 350; 546/118

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/248, 249, 262, 303; 544/236, 265, 276, 350; 546/118

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CRANK et al., Photochemistry of Heterocycles. III* Photolysis of Various 2-Substituted Benzimidazoles, Australian Journal of Chemistry, 1982, Vol. 35, No. 4, pages 775-784, especially example 5, page 777.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 2001 (21.09.2001)	25 OCT 2001

Name and mailing address of the ISA/US	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1998)